AWARD NUMBER: W81XWH-17-2-0043

TITLE: **Prostate Cancer Clinical Trials Consortium Clinical Research Site: University of Washington**

PRINCIPAL INVESTIGATOR: Heather Cheng, MD, PhD

CONTRACTING ORGANIZATION: University of Washington

REPORT DATE: JANUARY 2023

TYPE OF REPORT: Final Report

PREPARED FOR: arcU.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012
nd Development Command Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
JANUARY 2023	Final Report	30Sep2017 - 29Sep2022

4. TITLE AND SUBTITLE

Prostate Cancer Clinical Trials Consortium Clinical Research Site: University of Washington

5a. CONTRACT NUMBER
W81XWH-17-2-0043

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Heather Cheng, MD, PhD

E-Mail: hhcheng@uw.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER
NA

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

University of Washington
4333 Brooklyn Ave NE
Seattle, WA 98195-0001

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND

U.S. Army Medical Research and Development Command

Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Purpose: Participate as an active and productive member of the Prostate Cancer Clinical Trial Consortium (PCCTC) throughout the funding period.
Scope: This report summarizes total site activities for the University of Washington (UWash) for the funding period 30Sep2017-29Sep2022.
Major Progress: UWash was the lead/co-lead site on 19 trials in which we participated during this funding period.
Results: UWash accrued 5 patients to PCCTC trials, proposed 11 LOIs, and accrued 52 patients (1 .5%) from a DAP.
Significance: The PCCTC provides a mechanism for participation in early clinical development of novel agents and rapid testing of these agents for the treatment of prostate cancer. Many of the PCCTC trials have challenging entry criteria such as a biopsy of metastatic tissue or complicated pharmacokinetics/pharmacodynamics, and collection of correlative biomarkers. The PCCTC is well positioned to conduct such trials that might not be possible outside of sites that specialize in prostate cancer translational research. Shortening drug development time with better trial design, patient selection, and validation of biomarkers will bring new agents to prostate cancer patients faster, optimize treatment for the individual patient, and avoid treating others with ineffective therapies.

15. SUBJECT TERMS
Prostate cancer, castration resistant, phase I/II, immunotherapy, novel agent, androgen receptor, biopsy, circulating tumor cells, germline genetics

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRDC
U	U	U	UU	751	19b. TELEPHONE NUMBER *(include area code)*

Table of Contents

1. **INTRODUCTION:**
The University of Washington (UWash) has been a member of the Department of Defense Prostate Cancer Clinical Trials Consortium (PCCTC) since 2006. The purpose of the PCCTC is to provide a mechanism for collaboration among institutions with specialized expertise in prostate cancer in order to develop new agents and combinations of drugs in phase 1 and 2 trials. The mission of the PCCTC is aligned with that of the CDMRP: to eliminate deaths from prostate cancer and to enhance the well-being of men experiencing the impact of prostate cancer.

2. **KEYWORDS:**
Prostate cancer, castration resistant, phase I/II, immunotherapy, novel agent, androgen receptor, biopsy, circulating tumor cells, germline genetics

3. **ACCOMPLISHMENTS:**
   a. **What were the major goals of the project?**
      i. Accrue at least 25 patients per year to PCCTC trials
      ii. Accrue at least 5% patients from disproportionately affected populations per year
      iii. Propose a minimum of two trials per year or eight trials over 4 years, which may include biomarker studies
      iv. Participate in a minimum of eight trials initiated by other sites over 4 years
      v. Ensure timely submission of quality data
      vi. Participate in ≥1 PCCTC committee
      vii. Attend all face-to-face meetings of the PCCTC
      viii. Participate in scheduled consortium conference calls
      ix. Participate in review meetings/evaluation by the External Advisory Board (EAB)
      x. Compliance with the operations manual of the Consortium regarding tasks such as (but not limited to): publication of major findings, intellectual and material property issues, quality assurance and control procedures, data submission and management plans

   b. What was accomplished under these goals?
      i. Site accrued 359 patients to PCCTC trials, 93 patients to therapeutic and 266 patients to non-therapeutic trials. See Appendix 1 for details.
      ii. 52 of 359 patients (14.5%) accrued during this reporting period were members of disproportionately affected populations, including 18 (5%) Vietnam era veterans.
      iii. Site submitted the following LOIs (11) in this award period: c18-211, c19-244 (jointly submitted with OHSU), c19-248, c20-258, c20-259, c21-271, c21-274, c21-275, c21-295 (jointly submitted with Columbia), c22-297 (jointly submitted with Columbia), and c22-303.
      iv. Site participated in 26 PCCTC trials: 7 trials initiated by other PCCTC sites, 8 initiated by UWash with another site, and 11 initiated by UWash. In addition, 2 trials initiated by UWash with another site were in start-up at the end of the award period.
      v. Site met requirements of timely submission of quality data.
      vi. Dr. Cheng [PI] is the Chairperson and Dr. Yu [co-PI] is a member of the Germline Genetics Working Group. Drs. Cheng and Yu are also members of the Recognizing/Tackling Disparities Working Group.

vii. PCCTC meetings at GU ASCO, ASCO, and PCF were attended by Drs. Cheng, Yu and Schweizer. (Former PI, Dr. Higano, also attended meetings until her retirement in June 2020.)
viii. Coordinator participates in site conference calls. PI and/or co-I and sub-investigators participate in all monthly PI conference calls.
ix. All EAB meetings were attended by PI [Cheng &/or Higano]. Co-PIs [Yu &/or Schweizer] also attended the EAB meeting beginning year 2 of award period.
x. Procedures are in place and the UWash site is in compliance with the operations manual of the PCCTC.

c. **What opportunities for training and professional development has the project provided?**

Junior faculty members have had the opportunity to meet senior leaders of the PCCTC and to benefit academically from these contacts. The PI, Dr. Cheng, was nominated to chair the PCCTC Germline Genetics Working Group. She led the development, and is the senior or co-senior author, of three PCCTC-led papers on this topic, which have also featured junior investigators and thus opportunities for other faculty to become more involved in prostate cancer genetics. Dr. Cheng's participation in the PCCTC helped accelerate her reputation as a recognized international expert in germline genetics in prostate cancer. Dr. Cheng is also partnering with Dr. Channing Paller at Johns Hopkins, together with PCCTC, to lead the PROMISE prostate cancer genetics registry.

Dr. Schweizer is leading "A Phase II Trial of Durvalumab and Olaparib for treatment of biochemically-recurrent prostate cancer in men predicted to have a high neoantigen load" (LOI in process). The study was presented by Dr. Alexandra Sokolova (UWash former mentee, now faculty at OHSU) on 8/20/2020 at Monthly PI Call). The trial will also be conducted by Dr. Jacob Berman (DFCI). In addition, Drs. Schweizer and Sokolova have discussed with Dr. Karen Autio of MSKCC and PI of PCCTC trial c17-192 about opportunities for collaborating on biomarker studies from respective studies.

UWash has recruited several new faculty members whose training and careers will benefit from participation in the PCCTC: Dr. Emily Weg is a radiation oncologist who was recruited to UWash from MSKCC. She is interested in germline genetics and somatic biomarkers as related to radiation treatment selection, response and resistance. She has become involved with the Germline Genetics Working Group and she will be site PI for the c20-252 DASL-HICAP study.

Dr. Jessica Hawley is a medical oncologist recently recruited to UWash (started 9/2021) from Columbia, where she was mentored by Drs. Charles Drake and Mark Stein. She has expertise in prostate cancer clinical research and is particularly interested in the immunomodulatory effects of androgen signaling and inhibition. Drs. Yu, Schweizer and Cheng are helping her find and develop research interests and career opportunities.

Moreover, recent UWash fellows have gone on to accept prestigious academic faculty positions at other institutions, including PCCTC site OHSU (Dr. Sokolova), University of Colorado (Dr. Laura Graham), University of Pittsburg (Dr. Risa Wong), and Stanford (Dr. Ali Khaki). Thus, PCCTC participation has fostered both

collaboration and academic growth for trainees and junior faculty at our institution, the larger PCCTC and prostate cancer research community.

d. **How were the results disseminated to communities of interest?**
We believe that informed patients make the best decisions, are more satisfied, and have the best outcomes. To that end, we have a long history of educating patients about prostate cancer, the role of clinical research, and new treatments available, not only at our institution, but around the country. We have typically two annual meetings directed at men with prostate cancer:

The Institute for Prostate Cancer Research (IPCR) at UWash was founded to develop interdisciplinary institutional programs for prostate cancer research. In addition to fund-raising, the meeting reports on the status of research endeavors in prostate cancer to the lay public.

Dr. Yu is the Director of the Clinical Core of the PC SPORE grant and continues the SPORE Advocates Committee. This committee is engaged in numerous outreach activities in the Pacific Northwest and includes consumer advocates from Vancouver, BC, Seattle, WA and Portland, OR. Members of this committee participate in the SPORE lecture series as well as the SPORE external advisory board meetings where they hear results from SPORE related clinical trials and basic research.

Drs. Cheng, Schweizer and Yu, as well as their colleagues Drs. Montgomery, Nyame, Gore, Lin, Wright, and others are also actively engaged in educational and CME activities, particularly around their research topics of interest and clinical trials. Faculty at UWash are regularly invited to speak at monthly prostate cancer support groups in Washington (Seattle, Tacoma, Olympia, Shelton, Centralia), Oregon (Portland), and British Columbia (Vancouver).

e. **What do you plan to do during the next reporting period to accomplish the goals?**
Nothing to Report.

4. **IMPACT:**
   a. **What was the impact on the development of the principal discipline(s) of the project?**
   Investigators at UWash and other PCCTC institutions continue to focus on the evolving role of genetics and genomics in prostate cancer. Our group has driven changes in NCCN guidelines since 2019 and published extensively with the PCCTC Germline Genetic Working Group and through efforts such as the PROMISE registry. In addition, our efforts also include developing better diagnostic strategies for precision oncology, including recent publication led by Dr. Schweizer on concordance between primary prostate tumor and metastases that will inform testing for PARPi candidacy.

   To provide needed genetics expertise in the clinic, Dr. Cheng organized a unique prostate cancer genetics clinic at UWash, and leads both UWash and PCCTC efforts in this area. She chairs the PCCTC Prostate Cancer Genetics Working Group and is PI of the GENTleMEN study that enables men with prostate cancer to enroll on the trial to receive free germline testing.

b. **What was the impact on other disciplines?**
- Provide guidance to primary care physicians and urologists on the importance of complete family history and education about germline genetic testing.
- Educate oncologists, urologists and radiation oncologists about germline genetic testing for understanding cancer risk versus tumor biomarker testing for treatment decisions.
- Developing more education in radiation oncology (with help of Dr. Weg).
- Address the critical role for genetic counseling of prostate cancer patients with pathogenic germline mutations.
- Provide a model of care to meet the need for genetics expertise in prostate cancer in the clinic.
- Develop infrastructure to help identify more rare germline variants with prostate cancer.

c. **What was the impact on technology transfer?**
Nothing to Report.

d. **What was the impact on society beyond science and technology?**
NCCN guidelines for prostate cancer therapy were amended based on work that came out of PCCTC involvement in early development of enzalutamide, abiraterone, radium-223, rucaparib and Olaparib, and input from members of the PCCTC, including the PI, who are on the Prostate Panel of the NCCN. In addition, guidelines around germline genetic testing and tumor sequencing and liquid biopsies have also arisen from work from our group. We are also focused on therapeutic strategies to address treatment emergent disease, further developing immunotherapeutic approaches, and incorporating novel imaging and theranostics, each of which has potential to reduce the impact of suffering from prostate cancer.

5. **CHANGES/PROBLEMS:**
a. **Changes in approach and reasons for change**
Nothing to Report.

b. **Actual or anticipated problems or delays and actions or plans to resolve them**
Nothing to Report.

c. **Changes that had a significant impact on expenditures**
Nothing to Report.

d. **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**
Nothing to Report.

6. **PRODUCTS:**
a. Publications, conference papers, abstracts, and presentations (<u>UWash author)</u>

Abstracts:

Armstrong AJ, Lin P, <u>Higano CS</u>, Iversen P, Sternberg CN, Tombal B, Phung D, Parli T, Krivoshik A, Beer TM. Prognostic Associates of Prostate-Specific Antigen (PSA) Decline With Survival, Radiographic Response and Progression in Chemotherapy-Naïve Men With Metastatic Castration-Resistant Prostate Cancer (mCRPC) Treated

With Enzalutamide. Abstract #2105. Submitted for presentation, ESMO Congress 2017, Madrid, Spain, September 2017.

Beer TM, Chowdhury S, Saad F, Shore, ND, Higano CS, Iversen P, Fizazi K, Miller K, Heidenreich A, Kim CS, Phung D, Barrus J, Nikolayeva N, Krivoshik A, Waksman J, Tombal B. Hepatic effects assessed by review of safety data in enzalutamide castration-resistant prostate cancer (CRPC) trials. *J Clin Oncol* 36, 2018 (suppl 6S; abstr 199). Poster presentation, ASCO 2018 Genitourinary Cancers Symposium, San Francisco, CA, February 2018.

Mateo J, Cheng HH, Beltran H, Dolling D, Xu W, Pritchard C, Mossop H, Rescigno P, Perez-Lopez R, Sailer V, Kolinsky MP, Balasopoulou A, Bertran C, Carreira S, Thorne H, Montgomery RB, Sandhu SK, Rubin MA, Nelson P, De Bone JS. Clinical outcome of patients with germline DNA repair mutations: Results from a retrospective international study. *J Clin Oncol* 36, 2018 (suppl 6S; abstr 218). Poster presentation, ASCO 2018 Genitourinary Cancers Symposium, San Francisco, CA, February 2018.

McKay RR, Xie W, Lis R, Ye H, Zhang Z, Trinh QD, Chang SL, Harshman LC, Ross A, Pienta KJ, Lin DW, Ellis WJ, Montgomery RB, Chang P, Wagner A, Bubley G, Kibel AS, Taplin ME. Results of a phase II trial of neoadjuvant abiraterone + prednisone + enzalutamide + leuprolide (APEL) versus enzalutamide + leuprolide (EL) for patients with high-risk localized prostate cancer (PC) undergoing radical prostatectomy (RP). . *J Clin Oncol* 36, 2018 (suppl 6S; abstr 79). Poster presentation, ASCO 2018 Genitourinary Cancers Symposium, San Francisco, CA, February 2018.

Lim DM, Gulati R, Aleshin-Guendel S, Cheng HH, Gawne AM, Wingate JT, Etzioni RD, Yu EY. Proportion of biochemically-recurrent prostate cancer patients with durable undetectable PSA after short-course androgen deprivation therapy. *J Clin Oncol* 36, 2018 (suppl 6S; abstr 207). Poster presentation, ASCO 2018 Genitourinary Cancers Symposium, San Francisco, CA, February 2018.

Yu EY, Gulati R, Aleshin-Guendel S, Cheng HH, Gawne AM, Wingate JT, Etzioni RD, Lim DM. Association of undetectable PSA with time to metastasis and survival after short-course androgen deprivation therapy for biochemically-recurrent prostate cancer patients. *J Clin Oncol* 36, 2018 (suppl; abstr e17073). ASCO Annual Meeting, Chicago, IL, June 2018.

Shore ND, Heath EI, Nordquist LT, Cheng HH, Bhatt K, Morrow M, McMullan T, Kraynyak K, Lee J, Sacchetta B, Liu L, Rosencranz S, Tagawa ST, Parikh RA, Tutrone RF, Garcia JA, Whang YE, Kelly WK, Csiki I, Bagarazzi ML. Evaluation of an immunotherapeutic DNA-vaccine in biochemically relapsed prostate cancer. *J Clin Oncol* 36, 2018 (suppl; abstr 5078). Poster presentation, ASCO Annual Meeting, Chicago, IL, June 2018.

Cheng HH, Bowen D, Klemfuss N, Sievers CM, Kang SH, Zhou A, Pritchard C, Nelson P, Montgomery RB. The GENTleMEN study: Genetic testing for men with metastatic prostate cancer in Washington state and beyond. *J Clin Oncol* 36, 2018 (suppl; abstr TPS5098). Poster presentation, ASCO Annual Meeting, Chicago, IL, June 2018.

Graff JN, Beer TM, Alumkal JJ, Kreitner D, Petreaca D, Thomas GV, Cheng HH. c15-148: Phase I/II trial of concurrent chemohormonal therapy using enzalutamide and cabazitaxel in patients with metastatic castration resistant prostate cancer (mCRPC). *J Clin Oncol* 36, 2018 (suppl; abstr TPS5097). Poster presentation, ASCO Annual Meeting, Chicago, IL, June 2018.

Rathkopf DE, Autio KA, Antonarakis ES, Cheng HH, Arauz G, Slack A, Hullings M, Scher HI, Feng FY, Knudsen KE. c15-160: Enzalutamide (ENZA) plus CC-115 in men with metastatic castration-resistant prostate cancer (mCRPC): A phase 1b Prostate Cancer Clinical Trials Consortium study. *J Clin Oncol* 36, 2018 (suppl; abstr 5045). Poster presentation, ASCO Annual Meeting, Chicago, IL, June 2018.

De Bono JS, Higano C, Saad F, Miller K, Casey M, Czibere A, Healy C, Fizazi K. TALAPRO-1: An open-label, response rate phase II study of talazoparib (TALA) in men with DNA damage repair defects (DDR) and metastatic castrationresistant prostate cancer (mCRPC) who previously received taxane-based chemotherapy (CT) and progressed on > 1 novel hormonal therapy (NHT). *Ann of Oncol* (2018) 29 (suppl 8). Poster presentation. ESMO Congress 2018, Munich Germany. October 2018.

De Bono JS, Hansen A, Choudhury AD, Cook N, Heath EI, Higano C, Linch M, Martin-Liberal J, Rathkopf DE, Wisinski KB, Barry S, de Bruin E, Brugger W, Colebrook S, Klinowska T, Moschetta M, Mortiner PGS, Siu LL, Shapiro G. AZD8186, a potent and selective inhibitor of PI3Kb/d, as monotherapy and in combination with abiraterone acetate plus prednisone (AAP), in patients (pts) with metastatic castrate-resistant prostate cancer (mCRPC). *Ann of Oncol* (2018) 29 (suppl 8). Poster presentation. ESMO congress 2018, Munich Germany. October 2018.

Yu EY, Massard C, Retz M, Tafreshi A, Galceran JC, Hammerer P, Fong PCC, Shore N, Joshua A, Linch MD, Gurney H, Romano E, Augustin M, Piulats JM, Wu H, Schloss C, Poehlein CH, De Bono JS. KEYNOTE-365 Cohort A: Pembrolizumab plus olaparib in docetaxel-pretreated patients with metastatic castrate-resistant prostate cancer. *J Clin Oncol* 37, 2019 (suppl 7S; abstr 145). Oral presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2019

Smith MR, Sandhu SK, Kelly WK, Scher HI, Efstathiou E, Lara P, Yu EY, George DJ, Chi KN, Summa J, Kothari N, Zhao X, Espina BM, Ricci DS, Simon JS, Tran N, Fizazi K, GALAHAD Investigators. Phase II study of niraparib in patients with metastastic castration-resistant prostate cancer and biallelic DNA-repair gene defects: Preliminary results of GALAHAD. *J Clin Oncol* 37, 2019 (suppl 7S; abstr 202). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2019

Massard C, Retz M, Hammerer P, Quevedo F, Fong PCC, Berry WR, Gurnery H, Piulats JM, Joshua A, Linch MD, Kolinsky M, Romano E, Sridhar SS, Conter HJ, Augustin M, Wu, H, Schloss C, Poehlein CH, Yu EY. KEYNOTE-365 Cohort B: Pembrolizumab plus docetaxel and prednisone in abiraterone or enzalutamide-pretreated patients with metastatic castration-resistant prostate cancer. *J Clin Oncol* 37, 2019 (suppl 7S; abstr 170). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2019

Fong PCC, Retz M, Drakaki A, Massard C, Berry WR, Romano E, Bono JS, Feyerabend S, Appleman LJ, Conter HJ, Sridhar SS, Shore ND, Linch MD, Joshua A, Gurney H, Wu, H, Schloss C, Poehlein CH, Yu EY. KEYNOTE-365 Cohort C: Pembrolizumab plus enzalutamide in abiraterone-pretreated patients with metastatic castration-resistant prostate cancer. *J Clin Oncol* 37, 2019 (suppl 7S; abstr 171). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2019

Yu, E. KEYNOTE-365 Cohort A: Pembrolizumab plus olaparib in docetaxel-pretreated patients with metastatic castration-resistant prostate cancer. *eCancerTV*. February 18, 2019. https://ecancer.org/video/7697/keynote-365-cohort-a--pembrolizumab-plus-olaparib-in-docetaxel-pretreated-patients-with-mcrpc.php

Yu, E. Results from KEYNOTE-365 in metastatic castration resistant prostate cancer. *OBRoncology*. February 22, 2019. https://www.youtube.com/watch?v=jJm_DQrHwIc

Yu, E. Results from KEYNOTE 365 in metastatic castration-resistant prostate cancer. *OncologyTube*. March 20, 2019. https://www.oncologytube.com/video/results-from-keynote-365-in-mcrpc

Yu EY, Massard C, Retz M, Tafreshi A, Carles J, Hammerer P, Fong PCC, Shore N, Joshua AM, Linch MD, Gurney H, Romano E, Augustin M, Piulats JM, Wu H, Schloss C, Poehlein CH, De Bono JS. Pembrolizumab plus olaparib in docetaxel-pretreated patients with metastatic castrate-resistant prostate cancer: Cohort A of the phase 1b/2 KEYNOTE-365 study. *J Clin Oncol* 37, 2019 (suppl; abstr 5027). Poster presentation at ASCO Annual Meeting, Chicago, IL, Jun. 2019

Fong PCC, Retz M, Drakaki A, Massard C, Berry WR, Romano E, Bono JS, Feyerabend S, Appleman LJ, Conter HJ, Sridhar SS, Shore ND, Linch MD, Joshua A, Gurney H, Wu, H, Schloss C, Poehlein CH, Yu EY. Pembrolizumab plus enzalutamide in abiraterone-pretreated patients with metastatic castration-resistant prostate cancer: Cohort C of the phase 1b/2 KEYNOTE-365 study. *J Clin Oncol* 37, 2019 (suppl; abstr 5010). Poster Discussion Session at ASCO Annual Meeting, Chicago, IL, Jun. 2019

Massard C, Retz M, Hammerer P, Quevedo F, Fong PCC, Berry WR, Gurnery H, Piulats JM, Joshua A, Linch MD, Kolinsky M, Romano E, Sridhar SS, Conter HJ, Augustin M, Wu, H, Schloss C, Poehlein CH, Yu EY. Pembrolizumab plus docetaxel and prednisone in abiraterone or enzalutamide-pretreated patients with metastatic castration-resistant prostate cancer: Cohort B of the phase 1b/2 KEYNOTE-365 study. *J Clin Oncol* 37, 2019 (suppl; abstr 5029). Poster presentation at ASCO Annual Meeting, Chicago, IL, Jun. 2019

Pinder DM, Tombal BF, Armstrong AJ, Barrus JK, Beer TM, Evans CP, Heidenreich A, Higano CS, Kamba T, Lin P, Nikolayeva N, Sugg J, Steinberg JL, Tapin ME. Adverse Events of Special Interest Assessed by Review of Safety Data in Enzalutamide Castration-Resistant Prostate Cancer (CRPC) Trials. Presentation. 2019 SUNA urologic Conference, Lake Buena Vista, FL. September 2019.

Smith MR, Sandhu S, Kelly WK, Scher HI, Efstathiou E, Lara P, Yu EY, George DJ, Chi KN, Saad F, Summa J, Freedman JM, Mason GE, Zhu E, Ricci DS, Simon JS, Cheng S, Fizazi K. Pre-specified interim analysis of GALAHAD: A phase 2 study of niraparib in patients with metastatic castration-resistant prostate cancer and biallelic DNA-repair gene defects. *ESMO Congress* Abstract LBA50, 2019 European Society of Medical Oncology Congress. Barcelona, Spain, Sept. 2019. Poster presentation at ESMO Congress, Barcelona, Spain, Sept. 2019

George, D, Mucci, L, Rathkopf, D, Chi, K, Zhang, T, Barata, P, Cheng, H, Pomerantz, M, Dreicer, R, Alva, A, Ong, M, Heath, E, Enting, D, Whang, Y, Hotte, S, Bjartell, A, Fay, A, Omlin, A, Davis, I, Villanti, P, Vinson, J, Kantoff, P, First 500 patients of IRONMAN: International Registry for Men with Advanced Prostate Cancer. Prostate Cancer Foundation Annual Meeting, Carlsbad, CA (2019) [Abstract]

Mucci, L, Villanti, P, Vinson, J, Gold, T, Rathkopf, D, Chi, K, Zhang, T, Barata, P, Cheng, H, Pomerantz, M, Dreicer, R, Alva, A, Ong, M, Heath, E, Enting, D, Whang, Y, Hotte, S, Bjartell, A, Fay, A, Morgans, A, Paich, K, McReynolds, J, George, D, Kantoff, P, Patient Reported Outcomes among Men with Advanced Prostate Cancer: Results from the IRONMAN registry. Prostate Cancer Foundation Annual Meeting, Carlsbad, CA (2019) [Abstract]

Morris, MJ, De Wit, R, Vogelzang, NJ, Tagawa, ST, Higano, CS, A phase III trial of docetaxel versus docetaxel and radium-223 (Ra-223) in patients with metastatic castration-resistant prostate cancer (mCRPC): DORA. J Clin Oncol 38: 2020 (suppl; abstr TPS5594)

Graff, JN, Cheng, HH, Vuky, J, Alumkal, JJ, Kreitner, D, Petreaca, D, Grivas, P, Schweizer, MT, Higano, CS, Chen, Y, Yu, EY, Beer, TM, Phase II study of cabazitaxel (CAB) plus enzalutamide (ENZ) in metastatic castration-resistant prostate cancer (mCRPC). J Clin Oncol 38, 2020 (suppl 6; abstr 86)

Higano, CS, Saad, F, Sartor, AO, Miller, K, Conti, P, George, DJ, Sternberg, CN, Shore, ND, Sade, JP, Bellmunt, J, Smith, MR, Logothetis, C, Verholen, F, Kalinovsky, J, Bayh, I, Tombal, BF, Clinical outcomes and patient (pt) profiles in REASSURE: An observational study of radium-223 (Ra-223) in metastatic castration-resistant prostate cancer (mCRPC). J Clin Oncol 38, 2020 (suppl 6; abstr 32)

Aggarwal, RR, Alumkal, JJ, Szmulewitz, RZ, Higano, CS, Bryce, AH, Lopez-Gitlitz, A, McCarthy, SA, Miladinovic, B, McQuarrie, K, Thomas, S, Small, EJ, A randomized phase II study of apalutamide (APA), androgen deprivation therapy (ADT), or APA + ADT in patients (pts) with biochemically relapsed (BCR) prostate cancer (PC). J Clin Oncol 38, 2020 (suppl 6; abstr 320)

Morris, MJ, Fong, L, Petrylak, DP, Sartor AO, Higano, CS, Pagliaro, :LC, Alva, AS, Appleman, LJ, Tan, W, Vaishampayan, UN, Porcu, R, Tayama, D, Kadel, EE, Yuen, KCY, Datye, A, Armstrong, AJ, Safety and clinical activity of atezolizumab (atezo) + radium-223 dichloride (r-223) in 2L metastatic castration-resistant prostate cancer (mCRPC): Results from a phase Ib clinical trial. J Clin Oncol 38: 2020 (suppl; abstr 5565)

Sokolova, A, Marshall, CH, Lozano, R, Grivas, P, Higano, CS, Lotan, TL, Montgomery, RB, Nelson, P, Olmos, D, Schweizer, MT, Yezefski, TA,Yu, EY, Paller, CJ, Castro, E, Antonarakis, ES, Cheng, HH, Treatment response comparisons between ATM and BRCA2 germline carriers for mCRPC., J Clin Oncol 38, 2020 (suppl 6; abstr 63)

Francini, E, Montagnani, F, Nuzzo, PV, Gonzalez-Velez, M, Alimohamed, NS, Cigliola, A, Moreno, I, Rubio, J, Crivelli, J, Shaw, G, Petrioli, R, Bengala, C, Francini, G, Foncillas, JG, Sweeney, C, Higano, CS, Bryce, AH, Harshman, LC, Lee-Ying, R, Heng, DYC, Clinical outcomes of abiraterone acetate + prednisone (AA) + bone resorption inhibitors (BRI) versus AA alone as first-line therapy for castration-resistant prostate cancer (CRPC) with bone metastases (BM) in an international multicenter database, J Clin Oncol 38, 2020 (suppl 6; abstr 30)

Ledet, EM, Jaeger, E, Hatton, W, Moses, MW, Sokolova, AO, Nakazawa, M, Zhu, J., Dellinger, B, Elrefai, S, McKay, RR, Cheng, HH, Burgess, EF, Antonarakis, ES, Sartor, AO. Comparison of germline mutations in African American and Caucasian men with metastatic prostate cancer. *J Clin Oncol 38*, 2020 (suppl; abstr 5568). Poster presentation at American Society for Clinical Oncology Annual Meeting, virtual (2020).

Sokolova, AO, Miyamoto, AN, Pouv, DL, Cheng, HH, Montgomery, RB. Implementation of Systematic Germline Genetic Testing (GT) for Metastatic Prostate Cancer (mPC) Patients at the Puget Sound VA Prostate Oncology Clinic. *J Clin Oncol 38,* 2020 (suppl;abstr 1578). Poster presentation at American Society for Clinical Oncology Annual Meeting, virtual (2020).

Cheng, HH. *Germline Contribution to Metastatic Prostate Cancer.* Implementation of Genetic Testing for Inherited Prostate Cancer, Philadelphia Prostate Cancer Consensus Conference 2019, October 4, 2019.

Cheng, HH. *Prostate Cancer Genetics.* Prostate Cancer Foundation and UsTOO International Prostate Cancer Support Network, 26th Prostate Cancer Foundation Annual Scientific Retreat. Carlsbad, CA. October 26, 20019

Cheng, HH. *Molecular-Driven Therapy in GU Cancers.* 37th Annual CFS®: Innovative Cancer Therapy for Tomorrow, New York, NY. November 6, 2019.

Cheng, HH. *Men's Health—Prostate Cancer, DNA Repair Pathways and Predictive Testing for Inherited Cancers*. 9th Annual International Clinical Cancer Genetics and Genomics Conference, University of Chicago; Chicago, IL. April 18, 2020.

Cheng, HH. *Prostate Cancer Genetics.* Medscape CME Webinar; Seattle Cancer Care Alliance, Seattle WA. July 22, 2020.
https://www.medscape.org/viewarticle/937493

Loeb, S, Thakker, S, Falge, E, Taneja, S, Byrne, N, Walter, D, Katz, M, Wong, R, Leader, A, Selvan, P, Rose, M, Joy, M, Cheng, HH, Massey, P, and Giri, VN *Twitter Discussions about Genetic Testing and BRCA Awareness in the Context of Prostate*

Cancer and Breast Cancer. Prostate Cancer Foundation Annual Retreat, virtual (2020).

Rathkopf, D, Chi, KN, Olmos, D, Cheng, HH, Agarwal, N, Graff, J, Sandhu, S, Hayreh, V, Lopez-Gitlitz, A, Francis, P, Attard, G. AMPLITUDE: A Study of Niraparib (Nira) in Combination With Abiraterone Acetate and Prednisone (AAP) Versus AAP for the Treatment of Patients With Deleterious Germline or Somatic Homologous Recombination Repair (HRR) Gene-mutated Metastatic Castration-sensitive Prostate Cancer. Genitourinary Cancers Symposium, San Francisco, CA (2021).

Wong, RL, Cheng, HH, Holt, SK, Conrad, N, Fernandez, S, Sahoo, R, Bauer, Z, Toulouse, AE, Grivas, P, Yezefski, T, Russell, KJ, Wright, JL, Schweizer, MT, Montgomery, RB, Lee, JH, Chen, DL, Zeng, J, Lin, DW, Yu, EY. Use of Fluciclovine PET/CT (FluPET) for Prostate Cancer: Initial Results from a Prospective Registry at the University of Washington/Seattle Cancer Care Alliance. Genitourinary Cancers Symposium, San Francisco, CA (2021).

Loeb, S, Li, R, Sanchez Nolasco, T, Byrne, N, Cheng, HH, Leader, A, Giri, V. Barriers and Facilitators of Germline Genetic Evaluation for Prostate Cancer. Genitourinary Cancers Symposium, San Francisco, CA (2021).

Taza, F, Holler, A, Adra, N, Albany, C, Ashkar, R, Cheng, HH, Sokolova, AO, Agarwal, N, Nussenzveig, R, Bryce, A, Nafissi, N, Barata, P, Sartor, O, Bastos, D, Smaletz, O, Berchuck, J, Taplin, M, Aggarwal, R, Sternberg, C, Vlachostergios, PJ, Alva, AS, Su, C, Marshall, CH, Antonarakis, ES. Differential activity of PARP inhibitors in BRCA1- vs BRCA2-altered metastatic castration-resistant prostate cancer (mCRPC). Genitourinary Cancers Symposium, San Francisco, CA (2021).

Autio, KA, Higano, CS, Nordquist, LT, Appleman, LJ, Zhang, T, Zhu, X, Babiker, HM, Vogelzang, NJ, Prasad, S, Schweizer, MT, Billotte, S, Binder, J, Cavazos, N, Li, R, Chan, K, Cho, H, Dermyer, M, Hollingsworth, R, Kern, KA, Petrylak, DP. First-in-human, phase I study of PF-06753512, a vaccine-based immunotherapy regimen (PrCa VBIR), in biochemical relapse (BCR) and metastatic castration-resistant prostate cancer (mCRPC). DOI: 10.1200/JCO.2021.39.15_suppl.2612 *Journal of Clinical Oncology* 39, no. 15_suppl (May 20, 2021) 2612-2612.

Karzai, F, Couvillon, A, McKinney, Y, Lee-Wisdom, K, Choyke, PL, Giri, VN, Morgan, TM, Cheng, HH, Merino, MJ, Pinto, PA, Turkbey, B, Dahut, WL, A Natural History Study of Men with High-Risk Genetics for Prostate Cancer (PCa) Using Multiparametric MRI (mpMRI). American Association for Cancer Research Annual Meeting, Washington, D.C. (2021).

Rathkopf, DE, Chi, KN, Olmos, D, Cheng, HH, Agarwal, N, Graff, JN, Sandhu, SK, Hayreh, V, Lopez-Gitlitz, A, St. John, P, Attard, G, AMPLITUDE: A Study of Niraparib in Combination With Abiraterone Acetate Plus Prednisone (AAP) vs AAP Alone for the Treatment of Metastatic Castration-Sensitive Prostate Cancer (mCSPC) in Patients With Deleterious Germline orSomatic Homologous Recombination Repair (HRR) Gene Alterations. American Society for Clinical Oncology Annual Meeting, Chicago, CA (2021).

Zhao, JL, Antonarakis, ES, Cheng, HH, George, DG, Aggarwal, RA, Abida, W, Decker, B, Curley, T, Schonhoft, J, Haywood, S, Riedel, E, Carver, B, Wyatt, A,

Feng, FY, Knudsen, K, Rathkopf, D. A Phase 1b Study of Enzalutamide (Enza) plus CC-115 in Men with Metastatic Castration-Resistant Prostate Cancer (mCRPC). American Society for Clinical Oncology Annual Meeting, Chicago, CA (2021).

Wong, RL, Holt, SK, Zeng, J, Graham, L, Kang, R, Conrad, N, Toulouse, AE, Fernandez, S, Bauer, Z, Lai, MY, Yezefski, T, Wright, JL, Weg, ES, Hsieh, AC, Cheng, HH, Lee, JH, Chen, DL, Lin, DW, Yu, EY. The fluciclovine (FACBC) PET/CT site-directed therapy of oligometastatic prostate cancer (Flu-BLAST-PC) trial. American Society for Clinical Oncology Annual Meeting, Chicago, CA (2021).

Su, CT, Nizialak, E, Berchuck, JE, Vlachostergios, P, Ashkar, R, Sokolova, AO, Barata, P, Aggarwal, R, McClure, H, Sartor, O, Cheng, HH, Adra, N, Sternberg, CN, Taplin, ME, Cieslik, M, Antonarakis, E, Alva, A Differential responses to taxanes and PARP inhibitors (PARPi) in ATM- versus BRCA2-mutated metastatic castrate-resistant prostate cancer (mCRPC) patients (pts). American Society for Clinical Oncology Annual Meeting, Chicago, CA (2021).

Giri, VN, Walker, A, Gross, L, Fisher, C, Cheng, HH, Loeb, S. HELIX: Development and Testing of New Digital Tool to Facilitate Guideline-Concordant Prostate Cancer Genetic Testing in Clinical Practice. American Urological Association (2021).

Nordquist LT, Yu EY, Piulats JM, Gravis G, Fong PCC, Todenhoefer T, Laguerre B, Arranz Arija JA, Oudard S, Massard C, Stoeckle M, Carles J, Kolinsky MP, Augustin M, Gurney H, Tafreshi A, Li XT, Poehlein CH, Schloss C, de Bono JS. Pembrolizumab plus Olaparib in patients with docetaxel-pretreated metastatic castration-resistant prostate cancer: Updated results from KEYNOTE-365 cohort A with a minimum of 11 months of follow-up for all patients. Abstract MP24-14, 2021. Poster (virtual) presentation at the 2021 Annual Meeting of the American Urological Association Education and Research, Inc., Las Vegas, NV, September 2021.

Yu EY, Piulats JM, Gravis G, Fong P, Todenhofer T, Laguerre B, Arranz Arija J, Oudard S, Massard C, Stoeckle M, Nordquist LT, Carles J, Huang M, Li Y, Qiu P, Pohlein CH, Schloss C, de Bono J. Association between homologous recombination repair mutations and response to pembrolizumab plus Olaparib in metastatic castration-resistant prostate cancer: KEYNOTE 365 Cohort A biomarker analysis. *Annals of Oncology* (2021) 32 (suppl_5):S382-S406. Abstract 73P. ePoster presentation at ESMO Congress 2021.

Yu EY, Piulats JM, Gravis G, Fong PCC, Todenhofer T, Laguerre B, Arranz Arija JA, Oudard S, Massard C, Stoeckle M, Nordquist LT, Carles J, Kolinsky MP, Augustin M, Gurney H, Tafreshi A, Li XT, Pohlein CH, Schloss C, de Bono J. Pembrolizumab plus Olaparib in patients with docetaxel-pretreated metastatic castration-resistant prostate cancer: Update of KEYNOTE-365 cohort A with a minimum of 11 months of follow-up for all patients. *Annals of Oncology* (2021) 32 (suppl_5):S626-S677. Abstract 612P. ePoster presentation at ESMO Congress 2021.

Shore ND, Kramer G, Joshua AM, Li XT, Pohlein CH, Schloss C, de Bono JS, Yu EY. KEYNOTE-365 cohort I: Phase Ib/II study of platinum containing chemotherapy in combination with pembrolizumab and chemotherapy alone for treatment-emergent neuroendocrine prostate carcinoma. *Annals of Oncology* (2021) 32 (suppl_5):S626-S677. Abstract 639TiP. ePoster presentation at ESMO Congress 2021.

De Bono JS, Shore ND, Kramer G, Joshua AM, Li XT, Poehlein CH, Schloss C, Yu EY. Phase Ib/II trial of pembrolizumab + vibostolimab combination therapy in patients with adenocarcinoma metastatic castration-resistant prostate cancer or treatment-emergency neuroendocrine metastatic castration-resistant prostate cancer: KEYNOTE-365 cohorts G and H. *Annals of Oncology* (2021) 32 (suppl_5):S626-S677. Abstract 641TiP. ePoster presentation at ESMO Congress 2021.

Kramer G, Shore ND, Joshua AM, Li XT, Poehlein CH, Schloss C, de Bono JS, Yu EY. Phase 1b/II trial of pembrolizumab + Lenvatinib combination therapy in patients with adenocarcinoma metastatic castration-resistant prostate cancer or treatment-emergenct neuroendocrine metastatic castration-resistant prostate cancer. KEYNOTE-365 cohorts E and F. *Annals of Oncology* (2021) 32 (suppl_5):S626-S677. Abstract 640TiP. ePoster presentation at ESMO Congress 2021.

Yu EY, Pieczonka CM, Armstrong AJ, Suzuki H, Bailen JL, Murphy DG, Lebret T, Luz M, Thiery-Vuillemin A, Ortiz JA, Khan J, Briganti A. DARolutamide ObservationaL (DAROL) study in patients with nonmetastatic castration-resistant prostate cancer. *J Clin Oncol* 40, 2022 (suppl 16; abstr e17029).

Sokolova A, Gulati R, Cheng HH, Beer TM, Graff JN, Amador M, Toulouse A, Taylor K, Bailey S, Smith S, Tabatabaei S, Sinit R, Slottke R, Vuky J, Yezefski T, Grivas P, Yu EY, Schweizer MT. Durvalumab and Olaparib for the treatment of prostate cancer in men predicted to have a high neoantigen load. *J Clin Oncol* 40, 2022 (suppl 16; abstr TPS5099). Poster presentation at ASCO Annual Meeting, Chicago, IL, Jun. 2022.

Kramer G, de Bono J, Joshua AM, Shore ND, Zhu P, Poehlein CH, Schloss C, Yu EY. Phase 1b/2 study of pembrolizumab plus Lenvatinib, vibostolimab, or platinum-based chemotherapy for adenocarcinoma metastatic castration-resistant prostate cancer or neuroendocrine metastatic prostate cancer: KEYNOTE-365 cohorts E-I. Poster presentation at ESMO Congress 2022, Paris, France, Sept 2022**.**

Linch MD, Ferrario C, Stoeckle M, Laguerre B, Arranz J, Todenhofer T, Fong P, Piulats JM, Berry W, Emmenegger U, Mourey L, Mar N, Appleman L, Joshua AM, Conter H, Li XT, Schloss C, Poehlein C, de Bono JS, Yu EY. Two year follow-up of KEYNOTE-365 Cohort D: Pembrolizumab plus abiraterone acetate and prednisone in patients with chemotherapy-naïve metastatic castration-resistant prostate cancer. Poster presentation at ESMO Congress 2022, Paris, France, Sept 2022**.**

Lorentz, J, Appleman, L, Armstrong, AJ, Barata, P, DeMarco, TA, Dreicer, R, Elrod, JB, Fleming, M, George, C, Heath, EI, Hussain, MA, Mao, S, McKay, RR, Metwalli, A, Morgans, A, Orton, M, Pili, R, Saraiya, B, Sigmond, J, Sokolova, AO, Stadler, WM, Tran, C, Macario, N, Vinson, J, Green, R, Paller, CJ, Cheng, HH *Utilization of a decentralized national genetic registry to address informational needs caused by expanded testing recommendations and recently approved treatments for prostate cancer: the PROMISE Registry*. National Society for Genetic Counseling (2022) [Abstract]

Paller, CJ*, Barata, PC, Lorentz, J, Appleman, LJ, Armstrong, AJ, DeMarco, TA, Dreicer, R, Elrod, JB, Fleming, M, George, C, Heath, EI, Hussain, MH, Mao, S, McKay, RM, Metwalli, AR, Morgans, A, Stadler, WM, Tran, C, Macario, N, Vinson, J, Green, R, Cheng, HH* *PROMISE Registry: A Prostate Cancer Registry of Outcomes and Germline Mutations for Improved Survival and Treatment Effectiveness*. Prostate Cancer Foundation Annual Retreat (2022). [Poster abstract]

Schweizer, MT, Penkov, KD, Tolcher, AW, Choudhury, AD, Doronin, V, Aljumaily, R, Calvo, E, Frank, RC, Hamm, JT, Moreno Garcia, V, Vorobyev, V, Billotte, S, Bowler, T, Chen, J, Lin, T, Liu, L, Maity, A, Sharma, S & Johnson, ML. Phase I trial of PF-06821497, a potent and selective inhibitor of enhancer of zeste homolog 2 (EZH2), in follicular lymphoma (FL), small cell lung cancer (SCLC) and castration-resistant prostate cancer (CRPC). in ESMO Congress, Paris, France.

Markowski, MC, Wang, H, De Marzo, AM, Schweizer, MT, Antonarakis, ES & Denmeade, SR. Clinical Efficacy of Bipolar Androgen Therapy in Men with Metastatic Castration-Resistant Prostate Cancer and Combined Tumor-Suppressor Loss. Eur Urol Open Sci 41, 112-115 (2022).

Presentations:

Cheng, HH. *"Prostate Cancer Genetics: Testing, Targeted Therapy and Early Detection".* **Dana-Farber Genitourinary Oncology Seminar Series**, Boston, MA [invited faculty speaker]. October 14, 2020.

Cheng, HH. *"Genetics, Genomics, and Prostate Cancer".* **USToo International Webinar**, Chicago, IL. October 15, 2020. https://www.youtube.com/watch?v=WjkAF1xixOA&feature=youtu.be

Cheng, HH. Germline Genetics Working Group Update. **PCCTC Scientific Oversight Committee.** October 22, 2020

Cheng, HH. "*Genetic Testing in Prostate Cancer".* **Facing Our Risk of Cancer Empowered Annual Conference**, Philadelphia, PA. [invited faculty]. November 20, 2020. https://www.youtube.com/watch?v=m515URd9uYk&feature=youtu.be

Cheng, HH. Germline Genetics Working Group Update. **PCCTC Scientific Oversight Committee.** February 11, 2021

Giri VN, Walker A, Gross L, Fisher C, Cheng HH**,** Loeb, S. *HELIX: Development and Testing of New Digital Tool to Facilitate Guideline-Concordant Prostate Cancer Genetic Testing in Clinical Practice.* American Urological Association (2021).

Szymaniak BM, Facchini LA, Cheng HH**,** Morgans AK. *Integrating Genetic Counseling and Testing into Genitourinary (GU) Oncology & Urology Clinics.* BRCA Conference (2021).

Couvillon A, Karzai F, Choyke PL, Giri VN, Morgan TM, Cheng HH**,** Kesserwan C, Merino MJ, Pinto PA, Turkbey B, Dahut WL. *Inherited Risk for Prostate Cancer: How to Follow and Image the Natural History of Men with High-Risk Genetics*. BRCA Conference (2021).

Cheng HH, Powers J, Gulati R, Le A, Ledet E, Van Allen E, Vijai J, Nicolosi P, Nussbaum RL, Garber JE, Offit K, Schiffman J, Sartor O, Nelson PS, Walsh MF, Pritchard CC, Maxwell KN. *TP53 variants are associated with an increased risk of prostate cancer*. American Society of Human Genetics (2021).

Zhao JL, Antonarakis ES, *Cheng HH*, George DG, Aggarwal RA, Abida W, Decker B, Curley T, Schonhoft J, Anderson A, Haywood S, Riedel E, Carver B, Wyatt A, Feng FY, Knudsen K, Rathkopf D. *A Phase 1b Study of Enzalutamide (Enza) plus CC-115 in Men with Metastatic Castration-Resistant Prostate Cancer (mCRPC).* European Society of Medical Oncology (2021).

Selvan P, Leader A, Hunter A, Massey P, Cheng HH, Loeb S, Giri VN. *Assessing the Impact of Messaging about Prostate Cancer and Genetics on Facebook*. Prostate Cancer Foundation Annual Retreat, virtual (2021).

McKean M, Carabasi MH, Stein MN, Schweizer MT, Luke JJ, Narayan V, Parikh RA, Pachynski RK, Zhang J, Peddareddigari VGR, Winnberg J, Roberts A, Rosen J, Hufner P, Gladney W, Fountaine TJ, Chagin K. *Safety and early efficacy results from a phase 1, multicenter trial of PSMA-targeted armored CAR T cells in patients with advanced mCRPC*. Genitourinary Cancers Symposium, San Francisco, CA (2022).

Sokolova AO, Gulati R, Cheng HH, Beer T, Graff JN, Vuky J, Yezefski T, Grivas P, Yu EY, Schweizer MT. *Trial in progress: Durvalumab and Olaparib for the Treatment of Prostate Cancer in Men Predicted to Have a High Neoantigen Load.* Genitourinary Cancers Symposium, San Francisco, CA (2022).

Giri VN, Cheng HH, Paller C, Weg E, Johnson J, Gross L, Russo J, Loeb S. *Virtual Genetics Board for Enhancing Knowledge and Practice of Prostate Cancer Genetic Testing: The ENGAGEMENT Study.* Genitourinary Cancers Symposium, San Francisco, CA (2022).

Paller CJ, Lorentz J, DeMarco TA, Stadler WM, Armstrong AJ, Taplin M, Hussain MH, Pili R, Mao S, Elrod JB, Sokolova AO, Heath EI, McKay RM, Vinson J, Tran C, Macario N, Cook A, Chiang J, Cheng HH. *PROMISE Registry: A Prostate Cancer Registry of Outcomes and Germline Mutations for Improved Survival and Treatment Effectiveness.* Genitourinary Cancers Symposium, San Francisco, CA (2022).

Wong RL, Cheng HH, Fann JR, Hnida J, Chakoian M, Schenker Y, Yu EY, Gore JL. *Longitudinal Screening for Depression and Anxiety in Prostate Cancer and Association with Disease and Treatment Factors*. American Society of Clinical Oncology Annual Meeting (2022).

Khan HM, Wong RL, Darst BF, Pritchard CC, Nelson PS, Stanford JL, Lin DW, Cheng HH. *Cancer Registry-Based Recruitment of Men with Incident Metastatic Prostate Cancer and their First-Degree Male Relatives for Germline Genetic Testing: Genetic Information to Inform Treatment and Screening (GIFTS) Study*. American Society of Clinical Oncology Annual Meeting (2022).

Cheng HH. *Genetic Testing in Prostate Cancer: Understanding Clinical Implications for Early Detection, Localized Disease, and CRPC.* Annual Meeting of the American Urological Association, New Orleans, LA, May 2022.

Cheng HH. *AR and PARP: Partners in Crime.* American Society of Clinical Oncology 2022 Annual Meeting, Chicago, IL, Jun 2022.

Cheng HH. *Risk-Based Screening and Hereditary Prostate Cancer.* Breakthroughs in Prostate Cancer Research. Institute for Prostate Cancer Research Symposium; Seattle, WA, Jul 2022.

Yu EY, Park SH, Goh JC, Shin SJ, Mehra N, McDermott R, Sala Gonzalez N, Fong P, Greil R, Retz M, Sade JP, Huang YH, Begbie SD, Rey F, Kramer G, Suzuki H, Zhang J, Kim J, Poehlein C, Antonarakis ES. Pembrolizumab plus Olaparib vs. abiraterone or enzalutamide for patients with previously treated metastatic castration-resistant prostate cancer: Randomized open-label phase 3 KEYLYNK-010 study. **Oral presentation at ESMO Congress 2022**, Paris, France, Sept 2022**.**

b. **Journal publications (UWash author)**

Rathkopf DE, Smith MR, Ryan CJ, Berry WR, Shore ND, Liu G, Higano CS, Alumkal JJ, Hauke R, Tutrone RF, Saleh M, Chow Maneval E, Thomas S, Ricci DS, Yu MK, de Boer CJ, Trinh A, Kheoh T, Bandekar R, Scher HI, Antonarakis ES. Androgen receptor mutations in patients with castration-resistant prostate cancer treated with apalutamide. Ann Oncol. 2017 Sep 1;28(9):2264-2271. PMID: 28633425; PMCID: PMC5834046.

Alumkal JJ, Chowdhury S, Loriot Y, Sternberg CN, de Bono JS, Tombal B, Carles J, Flaig TW, Dorff TB, Phung, Forer D, Noonberg SB, Mansbach H, Beer TM, Higano CS. Effect of Visceral Disease Site on Outcomes in Patients With Metastatic Castration-resistant Prostate Cancer Treated With Enzalutamide in the PREVAIL Trial. Clin Genitourin Cancer. 2017 Oct;15(5):610-617.e3. Epub 2017 Mar 3. PMID: 28344102.

Hussain M, Daignault-Newton S, Twardowski PW, Albany C, Stein MN, Kunju LP, Siddiqui J, Wu YM, Robinson D, Lonigro RJ, Cao X, Tomlins SA, Mehra R, Cooney KA, Montgomery B, Antonarakis ES, Shevrin DH, Corn PG, Whang YE, Smith DC, Caram MV, Knudsen KE, Stadler WM, Feng FY, Chinnaiyan AM. Targeting Androgen Receptor and DNA Repair in Metastatic Castration-Resistant Prostate Cancer: Results From NCI 9012. J Clin Oncol. 2018 Apr 1;36(10):991-999. doi: 10.1200/JCO.2017.75.7310. Epub 2017 Dec 20. PubMed PMID: 29261439

McKay RR, Montgomery B, Xie W, Zhang Z, Bubley GJ, Lin DW, Preston MA, Trinh QD, Chang P, Wagner AA, Mostaghel EA, Kantoff PW, Nelson PS, Kibel AS, Taplin ME. Post prostatectomy outcomes of patients with high-risk prostate cancer treated with neoadjuvant androgen blockade. Prostate Cancer Prostatic Dis. 2017 Dec 20. doi: 10.1038/s41391-017-0009-6. [Epub ahead of print] PubMed PMID: 29263420

Mateo J, Cheng HH, Beltran H, Dolling D, Xu W, Pritchard CC, Mossop H, Rescigno P, Perez-Lopez R, Sailer V, Kolinsky M, Balasopoulou A, Bertan C, Nanus DM, Tagawa ST, Thorne H, Montgomery B, Carreira S, Sandhu S, Rubin MA, Nelson PS, de Bono JS. Clinical Outcome of Prostate Cancer Patients with Germline DNA

Repair Mutations: Retrospective Analysis from an International Study. Eur Urol. 2018 Jan 29. pii: S0302-2838(18)30019-8. doi: 10.1016/j.eururo.2018.01.010. [Epub ahead of print] PMID: 29429804

Cheng HH. The resounding effect of DNA repair deficiency in prostate cancer. Urol Oncol. 2018 Mar 16. pii: S1078-1439(18)30070-X. doi: 10.1016/j.urolonc.2018.02.014. [Epub ahead of print] PMID: 29555412

Hahn AW, Higano CS, Taplin ME, Ryan CJ, Agarwal N. Metastatic Castration-Sensitive Prostate Cancer: Optimizing Patient Selection and Treatment. Am Soc Clin Oncol Educ Book. 2018 May 23;(38):363-371. PMID: 30231388.

Rathkopf DE, Beer TM, Loriot Y, Higano CS, Armstrong AJ, Sternberg CN, de Bono JS, Tombal B, Parli T, Bhattacharya S, Phung, Krivoshik A, Scher HI, Morris MJ. Radiographic Progression-Free Survival as a Clinically Meaningful End Point in Metastatic Castration-Resistant Prostate Cancer: The PREVAIL Randomized Clinical Trial. JAMA Oncol. 2018 May 1;4(5):694-701. PMID: 29522174; PMCID: PMC5885186.

Carlo MI, Giri VN, Paller CJ, Abida W, Alumkal JJ, Beer TM, Beltran H, George DJ, Heath EI, Higano CS, McKay RR, Morgans AK, Patnaik A, Ryan CJ, Schaeffer EM, Stadler WM, Taplin M, Kauff ND, Vinson J, Antonarakis ES, Cheng HH. Evolving Intersection Between Inherited Cancer Genetics and Therapeutic Clinical Trials in Prostate Cancer; A White Paper From the Germline Genetics Working Group of the Prostate Cancer Clinical Trials Consortium. DOI: 10.1200/PO.18.00060 *JCO Precision Oncology* – published online August 16, 2018.

VanderWeele DJ, Antonarakis ES, Carducci MA, Dreicer R, Fizazi K, Gillessen S, Higano CS, Morgans AK, Petrylak DP, Sweeney CJ, Hussain M. Metastatic Hormone-Sensitive Prostate Cancer: Clinical Decision Making in a Rapidly Evolving Landscape of Life-Prolonging Therapy. J Clin Oncol. 2019 Sep 10:JCO1901595.

Labrecque MP, Coleman IM, Brown LG, True LD, Kollath L, Lakely B, Nguyen HM, Yang YC, da Costa RMG, Kaipainen A, Coleman R, Higano CS, Yu EY, Cheng HH, Mostaghel EA, Montgomery B, Schweizer MT, Hsieh AC, Lin DW, Corey E, Nelson PS, Morrissey C. Molecular profiling stratifies diverse phenotypes of treatment-refractory metastatic castration-resistant prostate cancer. J Clin Invest. 2019 Jul 30;130:4492-4505.

Paller CJ, Antonarakis ES, Beer TM, Borno HT, Carlo MI, George DJ, Graff JN, Gupta S, Heath EI, Higano CS, McKay RR, Morgans AK, Patnaik A, Petrylak DP, Rettig MB, Ryan CJ, Taplin ME, Whang YE, Vinson J, Cheng HH, Giri VN; Germline Genetic Testing in Advanced Prostate Cancer; Practices and Barriers: Survey Results from the Germline Genetics Working Group of the Prostate Cancer Clinical Trials Consortium. PCCTC Germline Genetics Working Group. Clin Genitourin Cancer. 2019 Aug;17(4):275-282.e1.

Cheng HH, Sokolova AO, Schaeffer EM, Small EJ, Higano CS. Germline and Somatic Mutations in Prostate Cancer for the Clinician. J Natl Compr Canc Netw. 2019 May 1;17(5):515-521. Review.

Morris MJ, Loriot Y, Sweeney CJ, Fizazi K, Ryan CJ, Shevrin DH, Antonarakis ES, Pandit-Taskar N, Deandreis D, Jacene HA, Vesselle H, Petrenciuc O, Lu C, Carrasquillo JA, Higano CS. Radium-223 in combination with docetaxel in patients with castration-resistant prostate cancer and bone metastases: a phase 1 dose escalation/randomised phase 2a trial. Eur J Cancer. 2019 Jun;114:107-116.

Beltran H, Hruszkewycz A, Scher HI, Hildesheim J, Isaacs J, Yu EY, Kelly K, Lin D, Dicker A, Arnold J, Hecht T, Wicha M, Sears R, Rowley D, White R, Gulley JL, Lee J, Diaz Meco M, Small EJ, Shen M, Knudsen K, Goodrich DW, Lotan T, Zoubeidi A, Sawyers CL, Rudin CM, Loda M, Thompson T, Rubin MA, Tawab-Amiri A, Dahut W, Nelson PS. The Role of Lineage Plasticity in Prostate Cancer Therapy Resistance. Clin Cancer Res. 2019 Jul 30.

Schweizer MT, Antonarakis ES, Bismar TA, Guedes LB, Cheng HH, Tretiakova MS, Vakar-Lopez F, Klemfuss N, Konnick EQ, Mostaghel EA, Hsieh AC, Nelson PS, Yu EY, Montgomery RB, True LD, Epstein JI, Lotan TL, Pritchard CC. Genomic Characterization of Prostatic Ductal Adenocarcinoma Identifies a High Prevalence of DNA Repair Gene Mutations. JCO Precis Oncol. 2019;3. Epub 2019 Apr 18.

Higano CS, Armstrong AJ, Sartor AO, Vogelzang NJ, Kantoff PW, McLeod DG, Pieczonka CM, Penson DF, Shore ND, Vacirca J, Concepcion RS, Tutrone RF, Nordquist LT, Quinn DI, Kassabian V, Scholz MC, Harmon M, Tyler RC, Chang NN, Tang H, Cooperberg MR. Real-World outcomes of sipuleucel-T treatment in PROCEED, a prospective registry of men with metastatic castration-resistant prostate cancer. Cancer. 2019 Dec 1;125(23):4172-4180. doi: 10.1002/cncr.32445. Epub 2019 Sep 4. PMID: 31483485; PMCID: PMC6856402.

Danila DC, Szmulewitz RZ, Vaishampayan U, Higano CS, Baron AD, Gilbert HN, Brunstein F, Milojic-Blair M, Wang B, Kabbarah O, Mamounas M, Fine BM, Maslyar DJ, Ungewickell A, Scher HI. Phase I Study of DSTP3086S, an Antibody-Drug conjugate Targeting Six-Transmembrane Epithelial Antigen of Prostate 1, in Metastatic Castration-Resistant Prostate Cancer. J Clin Oncol. 2019 Dec 20;37(36):3518-3527. doi: 10.1200/JCO.19.00646. Epub 2019 Nov 5. PMID: 31689155.

Aggarwal RR, Schweizer MT, Nanus DM, Pantuck AJ, Heath EI, Campeau E, Attwell S, Norek K, Snyder M, Bauman L, Lakhotia S, Feng FY, Small EJ, Abida W, Alumkal JJ. A Phase Ib/IIa Study of the Pan-BET Inhibitor ZEN-3694 in Combination with Enzalutamide in Patients with Metastatic Castration-resistant Prostate Cancer. Clin Cancer Res. 2020 Jul 21. doi: 10.1158/1078-0432.CCR-20-1707. Epub ahead of print. PMID: 32694156.

Giri VN, Knudsen KE, Kelly WK, Cheng HH, Cooney KA, Cookson MS, Dahut W, Weissman S, Soule HR, Petrylak DP, Dicker AP, AlDubayan SH, Toland AE, Pritchard CC, Pettaway CA, Daly MB, Mohler JL, Parsons JK, Carroll PR, Pilarski R, Blanco A, Woodson A, Rahm A, Taplin ME, Polascik TJ, Helfand BT, Hyatt C, Morgans AK, Feng F, Mullane M, Powers J, Concepcion R, Lin DW, Wender R, Mark JR, Costello A, Burnett AL, Sartor O, Isaacs WB, Xu J, Weitzel J, Andriole GL, Beltran H, Briganti A, Byrne L, Calvaresi A, Chandrasekar T, Chen DYT, Den RB, Dobi A, Crawford ED, Eastham J, Eggener S, Freedman ML, Garnick M, Gomella

PT, Handley N, Hurwitz MD, Izes J, Karnes RJ, Lallas C, Languino L, Loeb S, Lopez AM, Loughlin KR, Lu-Yao G, Malkowicz SB, Mann M, Mille P, Miner MM, Morgan T, Moreno J, Mucci L, Myers RE, Nielsen SM, O'Neil B, Pinover W, Pinto P, Poage W, Raj GV, Rebbeck TR, Ryan C, Sandler H, Schiewer M, Scott EMD, Szymaniak B, Tester W, Trabulsi EJ, Vapiwala N, Yu EY, Zeigler-Johnson C, Gomella LG. Implementation of Germline Testing for Prostate Cancer: Philadelphia Prostate Cancer Consensus Conference 2019. *J Clin Oncol* 2020; 38(24):2798-2811. Epub June 9, 2020. PMID: 32516092. PMCID: 7430215.

Szymaniak, BM, Facchini, LA, Giri, VN, Antonarakis, EA, Beer, TM, Carlo, MI, Danila, DC, Dhawan, M, George, D, Graff, JN, Gupta, S, Heath, EI, Higano, CS, Liu, G, Molina, AM, Paller, CJ, Patnaik, A, Petrylak, DP, Reichert, Z, Rettig, MB, Ryan, CJ, Taplin, ME, Whang, YE, Morgans, AK*, Cheng, HH**,** McKay, RR*. Practical Considerations and Challenges for Germline Genetic Testing in Prostate Cancer Patients: Recommendations from the Germline Genetics Working Group of the PCCTC. *JCO Oncology Practice.* 2020, Sept 28, *(*co-senior author*)

Sokolova AO, Cheng HH. Genetic Testing in Prostate Cancer. Curr Oncol Rep. 2020 Jan 23;22(1):5. doi: 10.1007/s11912-020-0863-6. PMID: 31974718.

Sokolova AO, Yu EY, Cheng HH. Honing in on PARPi Response in Prostate Cancer: from HR Pathway to Gene-by-Gene Granularity. Clin Cancer Res. 2020 Jun 1;26(11):2439-2440. doi: 10.1158/1078-0432.CCR-20-0707. Epub 2020 Mar 31. PMID: 32234758; PMCID: PMC7269828.

Schweizer, MT, Cheng, HH, Nelson, PS, Montgomery, R, Two steps forward and one step back for precision in prostate cancer treatment. *JCO.* 2020, Sept 8: JCO2001755.

Carlson, AS, Rigo I, Acevedo, RI, Lim, DM, Gulati, R, Gawne, A, Sokolova, AO, Cheng, HH, Nelson, PS, Montgomery, B, Yu, EY, Schweizer, MT. Impact of DNA damage repair mutations on treatment outcomes in men receiving conventional therapy for metastatic castration resistant prostate cancer (*in press, PLOS ONE)*

Aggarwal RR, Schweizer MT, Nanus DM, Pantuck AJ, Heath EI, Campeau E, Attwell S, Norek K, Snyder M, Bauman L, Lakhotia S, Feng FY, Small EJ, Abida W, Alumkal JJ. A Phase Ib/IIa Study of the Pan-BET Inhibitor ZEN-3694 in Combination with Enzalutamide in Patients with Metastatic Castration-resistant Prostate Cancer. *Clin Cancer Res*. 2020 Oct 15;26(20):5338-5347. doi: 10.1158/1078-0432.CCR-20-1707. Epub 2020 Jul 21. PubMed PMID: 32694156; PubMed Central PMCID: PMC7572827.

Szymaniak BM, Facchini LA, Giri VN, Antonarakis ES, Beer TM, Carlo MI, Danila DC, Dhawan M, George D, Graff JN, Gupta S, Heath E, Higano CS, Liu G, Molina AM, Paller CJ, Patnaik A, Petrylak DP, Reichert Z, Rettig MB, Ryan CJ, Taplin ME, Vinson J, Whang YE, Morgans AK, Cheng HH, McKay RR. Practical Considerations and Challenges for Germline Genetic Testing in Patients With Prostate Cancer: Recommendations From the Germline Genetics Working Group of the PCCTC. *JCO Oncol Pract*. 2020 Dec;16(12):811-819. doi: 10.1200/OP.20.00431. Epub 2020 Sep 28. PMID: 32986533; PMCID: PMC7735040.

Jensen K, Konnick EQ, Schweizer MT, Sokolova AO, Grivas P, Cheng HH, Klemfuss NM, Beightol M, Yu EY, Nelson PS, Montgomery B, Pritchard CC. Association of Clonal Hematopoiesis in DNA Repair Genes With Prostate Cancer Plasma Cell-free DNA Testing Interference. *JAMA Oncol*. 2021 Jan 1;7(1):107-110. doi: 10.1001/jamaoncol.2020.5161. PubMed PMID: 33151258; PubMed Central PMCID: PMC7645740.

DeLucia DC, Cardillo TM, Ang L, Labrecque MP, Zhang A, Hopkins JE, De Sarkar N, Coleman I, da Costa RMG, Corey E, True LD, Haffner MC, Schweizer MT, Morrissey C, Nelson PS, Lee JK. Regulation of CEACAM5 and Therapeutic Efficacy of an Anti-CEACAM5-SN38 Antibody-drug Conjugate in Neuroendocrine Prostate Cancer. *Clin Cancer Res*. 2021 Feb 1;27(3):759-774. doi: 10.1158/1078-0432.CCR-20-3396. Epub 2020 Nov 16. PubMed PMID: 33199493; PubMed Central PMCID: PMC7854497.

Denmeade SR, Wang H, Agarwal N, Smith DC, Schweizer MT, Stein MN, Assikis V, Twardowski PW, Flaig TW, Szmulewitz RZ, Holzbeierlein JM, Hauke RJ, Sonpavde G, Garcia JA, Hussain A, Sartor O, Mao S, Cao H, Fu W, Wang T, Abdallah R, Lim SJ, Bolejack V, Paller CJ, Carducci MA, Markowski MC, Eisenberger MA, Antonarakis ES. TRANSFORMER: A Randomized Phase II Study Comparing Bipolar Androgen Therapy Versus Enzalutamide in Asymptomatic Men With Castration-Resistant Metastatic Prostate Cancer. *J Clin Oncol*. 2021 Apr 20;39(12):1371-1382. doi: 10.1200/JCO.20.02759. Epub 2021 Feb 22. PubMed PMID: 33617303; PubMed Central PMCID: PMC8274807.

Ledet EM, Burgess EF, Sokolova AO, Jaeger EB, Hatton W, Moses M, Miller P, Cotogno P, Layton J, Barata P, Lewis BE, Nakazawa M, Zhu J, Dellinger B, Elrefai S, Nafissi NN, Egan JB, Shore N, McKay RR, Bryce AH, Cheng HH, Antonarakis ES, Sartor O. Comparison of germline mutations in African American and Caucasian men with metastatic prostate cancer. *Prostate*. 2021 May;81(7):433-439. doi: 10.1002/pros.24123. Epub 2021 Apr 1. PMID: 33792945; PMCID: PMC8252583.

Cheng HH. Molecular Subtyping in the Neoadjuvant Setting in Prostate Cancer: Envisioning the Possibilities. *Eur Urol*. 2021 Sep;80(3):304-305. doi: 10.1016/j.eururo.2021.04.029. Epub 2021 May 7. PMID: 33972096.

Sokolova AO, Marshall CH, Lozano R, Gulati R, Ledet EM, De Sarkar N, Grivas P, Higano CS, Montgomery B, Nelson PS, Olmos D, Schweizer MT, Yezefski TA, Yu EY, Paller CJ, Sartor O, Castro E, Antonarakis ES, Cheng HH. Efficacy of systemic therapies in men with metastatic castration resistant prostate cancer harboring germline ATM versus BRCA2 mutations. *Prostate*. 2021 Sep 13. doi: 10.1002/pros.24236. Epub ahead of print. PMID: 34516663.

Sokolova AO, Marshall CH, Lozano R, Gulati R, Ledet EM, De Sarkar N, Grivas P, Higano CS, Montgomery B, Nelson PS, Olmos D, Sokolov V, Schweizer MT, Yezefski TA, Yu EY, Paller CJ, Sartor O, Castro E, Antonarakis ES, Cheng HH. Efficacy of systemic therapies in men with metastatic castration resistant prostate cancer harboring germline ATM versus BRCA2 mutations. Prostate. 2021 Dec;81(16):1382-1389. doi: 10.1002/pros.24236. Epub 2021 Sep 13. PMID: 34516663; PMCID: PMC8563438.

Taza F, Holler AE, Fu W, Wang H, Adra N, Albany C, Ashkar R, Cheng HH, Sokolova AO, Agarwal N, Kessel A, Bryce A, Nafissi N, Barata P, Sartor AO, Bastos D, Smaletz O, Berchuck JE, Taplin ME, Aggarwal R, Sternberg CN, Vlachostergios PJ, Alva AS, Su C, Marshall CH, Antonarakis ES. Differential Activity of PARP Inhibitors in *BRCA1*- Versus *BRCA2*-Altered Metastatic Castration-Resistant Prostate Cancer. JCO Precis Oncol. 2021 Jul 22;5:PO.21.00070. doi: 10.1200/PO.21.00070. PMID: 34778690; PMCID: PMC8575434.

Martin NA, Tepper JE, Giri VN, Stinchcombe TE, Cheng HH, Javle MM, Konnick EQ. Adopting Consensus Terms for Testing in Precision Medicine. JCO Precis Oncol. 2021 Oct 6;5:PO.21.00027. doi: 10.1200/PO.21.00027. PMID: 34651094; PMCID: PMC8509918.

Sokolova A, Cheng H. Germline Testing in Prostate Cancer: When and Who to Test. Oncology (Williston Park). 2021 Oct 20;35(10):645-653. doi: 10.46883/ONC.2021.3510.0645. PMID: 34669358.

Maxwell KN, Cheng HH, Powers J, Gulati R, Ledet EM, Morrison C, Le A, Hausler R, Stopfer J, Hyman S, Kohlmann W, Naumer A, Vagher J, Greenberg SE, Naylor L, Laurino M, Konnick EQ, Shirts BH, AlDubayan SH, Van Allen EM, Nguyen B, Vijai J, Abida W, Carlo MI, Dubard-Gault M, Lee DJ, Maese LD, Mandelker D, Montgomery B, Morris MJ, Nicolosi P, Nussbaum RL, Schwartz LE, Stadler Z, Garber JE, Offit K, Schiffman JD, Nelson PS, Sartor O, Walsh MF, Pritchard CC. Inherited TP53 Variants and Risk of Prostate Cancer. Eur Urol. 2022 Mar;81(3):243-250. doi: 10.1016/j.eururo.2021.10.036. Epub 2021 Dec 1. PMID: 34863587; PMCID: PMC8891030.

Weise N, Shaya J, Javier-Desloges J, Cheng HH, Madlensky L, McKay RR. Disparities in germline testing among racial minorities with prostate cancer. Prostate Cancer Prostatic Dis. 2021 Nov 13:1–8. doi: 10.1038/s41391-021-00469-3. Epub ahead of print. PMID: 34775478; PMCID: PMC8590439.

Mostaghel EA, Marck BT, Kolokythas O, Chew F, Yu EY, Schweizer MT, Cheng HH, Kantoff PW, Balk SP, Taplin ME, Sharifi N, Matsumoto AM, Nelson PS, Montgomery RB. Circulating and Intratumoral Adrenal Androgens Correlate with Response to Abiraterone in Men with Castration-Resistant Prostate Cancer. Clin Cancer Res. 2021 Nov 1;27(21):6001-6011. doi: 10.1158/1078-0432.CCR-21-1819. Epub 2021 Aug 18. PMID: 34407973; PMCID: PMC8563401.

Smith MR, Scher HI, Sandhu S, Efstathiou E, Lara PN Jr, Yu EY, George DJ, Chi KN, Saad F, Ståhl O, Olmos D, Danila DC, Mason GE, Espina BM, Zhao X, Urtishak KA, Francis P, Lopez-Gitlitz A, Fizazi K; GALAHAD investigators. Niraparib in patients with metastatic castration-resistant prostate cancer and DNA repair gene defects (GALAHAD): a multicentre, open-label, phase 2 trial. Lancet Oncol. 2022 Mar;23(3):362-373. doi: 10.1016/S1470-2045(21)00757-9. Epub 2022 Feb 4. PMID: 35131040.

Muzi M, O'Sullivan F, Perk TG, Muzi JP, Mankoff DA, Jeraj R, Duan F, Yu EY. Whole-Body [^{18}F]-Fluoride PET SUV Imaging to Monitor Response to Dasatinib Therapy in Castration-Resistant Prostate Cancer Bone Metastases: Secondary Results from ACRIN 6687. Tomography. 2021 Apr 25;7(2):139-153. doi: 10.3390/tomography7020013. PMID: 33923126; PMCID: PMC8167705.

McKay RR, Kwak L, Crowdis JP, Sperger JM, Zhao SG, Xie W, Werner L, Lis RT, Zhang Z, Wei XX, Lang JM, Van Allen EM, Bhatt RS, Yu EY, Nelson PS, Bubley GJ, Montgomery RB, Taplin ME. Phase II Multicenter Study of Enzalutamide in Metastatic Castration-Resistant Prostate Cancer to Identify Mechanisms Driving Resistance. Clin Cancer Res. 2021 Jul 1;27(13):3610-3619. doi: 10.1158/1078-0432.CCR-20-4616. Epub 2021 Apr 13. PMID: 33849963; PMCID: PMC8254786.

Yu EY, Kolinsky MP, Berry WR, Retz M, Mourey L, Piulats JM, Appleman LJ, Romano E, Gravis G, Gurney H, Bögemann M, Emmenegger U, Joshua AM, Linch M, Sridhar S, Conter HJ, Laguerre B, Massard C, Li XT, Schloss C, Poehlein CH, de Bono JS. Pembrolizumab Plus Docetaxel and Prednisone in Patients with Metastatic Castration-resistant Prostate Cancer: Long-term Results from the Phase 1b/2 KEYNOTE-365 Cohort B Study. Eur Urol. 2022 Jul;82(1):22-30. doi: 10.1016/j.eururo.2022.02.023. Epub 2022 Apr 6. PMID: 35397952.

c. **Books or other non-periodical, one-time publications**
Nothing to report.

d. **Other publications, conference papers, and presentations**
Nothing to report.

e. **Website(s) or other Internet site(s)**
The following site is publicly accessible and includes presentations of the IPCR educational conferences for patients described above in section 3.d.
Institute for Prostate Cancer Research
https://www.fredhutch.org/en/research/institutes-networks-ircs/institute-for-prostate-cancer-research.html

f. **Technologies or techniques**
Nothing to Report.

g. **Inventions, patent applications, and/or licenses**
Nothing to Report.

h. **Other Products**
Nothing to Report

7. **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

a. **What individuals have worked on the project?**

Name:	Heather Cheng, MD, PhD
Person months worked:	5
Project Role:	Principal Investigator (01Jul2020-29Sep2022)
Contribution to project:	Responsible for site's overall performance, assure site's goals are met as outlined in the SOW, participate as a senior PCCTC member and mentor.

Name:	Celestia Higano, MD
Person months worked:	11
Project Role:	Principal Investigator (30Sep2017-30Jun2020)
Contribution to project:	Responsible for site's overall performance, assure site's goals are met as outlined in the SOW, participate as a senior PCCTC member and mentor.
Name:	Evan Yu, MD
Person months worked:	5
Project Role:	Co-Principal Investigator
Contribution to project:	Conduct and recruit to PCCTC clinical trials, participate in weekly research and monthly PCCTC protocol meetings, attend face-to-face PCCTC meetings.
Name:	Michael Schweizer, MD
Person months worked:	2
Project Role:	Co-Principal Investigator
Contribution to project:	Conduct and recruit to PCCTC clinical trials, participate in weekly research and monthly PCCTC protocol meetings, attend face-to-face PCCTC meetings.
Name:	Zoya Bauer
Person months worked:	6
Project Role:	Assistant CRC (01Dec2019-30Jun2020)
Contribution to project:	Participate in PCCTC conference calls. Oversee research team in management of protocol adherence and timeliness/quality of data collection. Support data and regulatory coordinators, ensuring data collection is accurate and timely, and that all regulatory procedures meet local IRB requirements.
Project Role:	PCCTC CRC (01Feb2021-03Dec2021)
Contribution to project:	Track trial accruals, LOI submissions, and provide updates to PCCTC. Serve as point person for PCCTC activities. Participate in PCCTC coordinator conference calls. Manage consortium budget and contract process, provide monthly reports, oversee start-up process for PCCTC clinical trials, and post award accounting of DOD contract. Assist PI and co-PIs with preparation and submission of required semi-annual and annual reports.
Name:	M Jackie Campbell
Person months worked:	3
Project Role:	PCCTC CRC (30Sep2017-15Jun2018)
Contribution to project:	Track trial accruals, LOI submissions, and provide updates to PCCTC. Ensure research team adherence to protocols, timeliness and quality of data collection. Serve as point person for PCCTC activities and participate in bi-weekly PCCTC conference calls.

Name:	Nathan Conrad
Person months worked:	3
Project Role:	Data Coordinator
Contribution to project:	Track and enter data, including enrollment demographics, for PCCTC studies. Set up research charts and work-flow plans, and ensure timely submission of quality data for all UWash PCCTC trials.

Name:	Kelly Crowder
Person months worked:	4
Project Role:	Asst PCCTC CRC (30Sep2017-30Jun2019)
Contribution to project:	Participate in bi-weekly PCCTC conference calls. Work with PCCTC CRC to ensure research team adherence to protocols. Support data and regulatory coordinators, ensuring data collection is accurate and timely, and that all regulatory procedures meet local IRB requirements.
Project Role:	PCCTC CRC (04Dec2021-29Sep2022)
Contribution to project:	Disseminate LOIs, review PCCTC protocols, and manage patient accruals on PCCTC trials. Ensure implementation of all consortium trials in accordance with timelines set by consortium, and that accrual goals are met, with special focus on disproportionately affected populations. Assist faculty in protocol logistics and CRF design for PCCTC trials.

Name:	Randall Davis
Person months worked:	6
Project Role:	Budget Startup Specialist (01Dec2019-29Sep2022)
Contribution to project:	Develop site budgets for PCCTC studies, and negotiate amendments based on protocol modifications as needed.

Name:	Tina Dinh
Person months worked:	2
Project Role:	Budget Startup Specialist (01May2018-15Aug2019)
Contribution to project:	Develop site budgets for PCCTC studies, and negotiate amendments based on protocol modifications as needed.

Name:	Sara Fernandez
Person months worked:	1
Project Role:	Correlative Science Coordinator (01Jan2020-30Jun2020)
Contribution to project:	Manage acquisition, delivery and storage of biological samples, and oversee collection, processing and mailing of samples per protocol specifications.

Name:	Anne Lee
Person months worked:	2
Project Role:	Regulatory Coordinator (01Jan2018-30Jan2019)
Contribution to project:	Manage IRB submissions and renewals for PCCTC studies.

Name:	Sarah Finkelstein
Person months worked:	10
Project Role:	Budget/Contract Manager (30Sep2017-31Jan2021)
Contribution to project:	Manage consortium budgets and contracts, provide monthly reports to PI and PCCTC CRC, oversee start-up process for PCCTC clinical trials, and post-award accounting of DOD contract. Assist PI and co-PI with preparation and submission of required semi-annual and annual reports.
Project Role:	PCCTC CRC (01Jul2020-31Jan2021)
Contribution to project:	Track trial accruals, LOI submissions, and provide updates to PCCTC. Serve as point person for PCCTC activities. Participate in PCCTC coordinator conference calls.
Project Role:	Operations Support (01Feb2021-29Sep2022)
Contribution to project:	Support PCCTC CRC in tracking accruals and LOI submissions. Serve as resource to UWash team with respect to DOD award requirements. Assist PI, co-PI and PCCTC CRC with preparation and submission of semi-annual and annual reports.

Name:	Michelle Haug
Project Role:	Interim PCCTC CRC (16Jun2018-30Jun2020)
Person months worked:	4
Contribution to project:	Track trial accruals, LOI submissions, and provide updates to PCCTC. Ensure research team adherence to protocols, and timeliness and quality of data collection. Serve as point person for PCCTC activities and articipate in PCCTC coordinator conference calls.

Name:	Sarah Kang
Person months worked:	3
Project Role:	Research Assistant (01Jan-30Jun2018)
Contribution to project:	Assist with filing and managing of regulatory documentation, subject demographic data, and report preparation.

Name:	Martha Lee
Person months worked:	3
Project Role:	Administrative Support (thru 15Mar2020)
Contribution to project:	Provide administrative support for consortium related activities for the PI and research team.

Name:	Hannah Loesch
Person months worked:	1
Project Role:	Research Coordinator (01Sep2021-29Sep2022)
Contribution to project:	Serve as a resource for the conduct of protocol specified laboratory correlative projects and overall protocol coordination for PCCTC studies.

Name:	Colin Sievers
Person months worked:	2
Project Role:	Research Coordinator (01Jan2021-31Jul2021)
Contribution to project:	Serve as a resource for the conduct of protocol specified laboratory correlative projects and overall protocol coordination for PCCTC studies.

b. **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**
Nothing to Report

c. **What other organizations were involved as partners?**
Nothing to Report

8. **SPECIAL REPORTING REQUIREMENTS**
Not applicable.

9. **APPENDICES:**

Appendix 1 – PCCTC trials, status and accruals at UWash clinical research site during funding period

Appendix 2 – Copies of original publications

Appendix 3 – Curricula vitae for Cheng (PI), Yu (co-PI) and Schweizer (sub-I)

APPENDIX 1

PCCTC trials, status, and accruals at UWash clinical research site

30Sep2017-29Sep2022

Table A UWash PCCTC Trials, Open and in Start-Up
9/30/2017-9/29/2022
(abbreviation mCRPC = metastatic castration resistant prostate cancer)

PCCTC# (UW#)	Trial Title	UWash Accrual	Status	Lead Site
c13-131 (UW13024)	A Phase I Multicenter Study to Assess… AZD8186 in Patients with Advanced CRPC…	6	Closed 11/2018	UWash
c14-146 (UW15029)	Phase 2 Study of VT-464 in Patients with Castration-Resistant Prostate Cancer…	0	Closed 2/2018	MSKCC
c15-148 (CC9279)	A Phase I/II Trial of Concurrent Chemohormonal Therapy Using Enzalutamide and Cabazitaxel in Patients with mCRPC	11	Closed 6/2019	UWash OHSU
c15-156 (CC9342)	A Randomized Phase II Study Comparing Bipolar Androgen Therapy vs Enzalutamide in Asymptomatic Men with mCRPC Transformer	3	Closed 9/2018	JHU
c15-157 (UW14052)	A Phase I Study of ES414 in Patients with Metastatic Castration-Resistant Prostate Cancer	1	Closed 11/2018	UCSF UWash
c15-160 (CC9767)	A Phase 1b Study of Enzalutamide plus CC-115 in Men with CRPC	4	Closed 2/2020	MSKCC
c15-161 (CC9389)	A Phase I Study of a DNA Vaccine Encoding Androgen Receptor Ligand-Binding Domain (AR LBD)… in Patients with Metastatic Prostate Cancer	2	Closed 12/2017	UWisc
c15-166 (UW18003)	A Phase 1 Safety and Tolerability Study of ZEN003694 in Combination with Enzalutamide in Patients with mCRPC	6	Closed 2/2019	UCSF
c16-169 (UW15030)	A Phase 1 Study… of Escalating Doses of a Vaccine Based Immunotherapy Regimen (VBIR) for Prostate Cancer	5	Closed 02/2021	UWash Duke MSKCC
c16-174 (CC10054)	Phase III Trial of Docetaxel vs Docetaxel and Radium-223 for mCRPC (DORA)	1	Closed 7/2020	MSKCC UWash
c16-181 (UW16081)	Phase Ib/II Trial of Pembrolizumab (MK-3475) Combination Therapies in… (mCRPC) (KEYNOTE-365)	13	Open	UWash
c17-187 (CC9297)	A Pilot Study of Mobilization and Treatment of Disseminated Tumor Cells in Men with Metastatic Prostate Cancer	0	Closed 6/2018	UWash
c17-188 (UW16010)	A Phase IB, Open-Label Study… of Atezolizumab in combination with Radium-223 Dichloride in Patients with CRPC…	0	Closed 7/2018	KCC

PCCTC# (UW#)	Trial Title	UWash Accrual	Status	Lead Site
c17-189 (UW16062)	A Phase 2 Efficacy and Safety Study of Niraparib in Men with mCRPC and DNA-Repair Anomalies	1	Closed 5/2020	UWash OHSU
c17-198 (UW17076)	A Multi-Center Trial… of Major Adverse Cardiovascular Events in Patients with Prostate Cancer and Cardiovascular Disease…PRONOUNCE	0	Closed 3/2020	MSKCC UWash
c18-211 (UW17031)	A Phase 2… Study of Talazoparib in Men with DNA Repair Defects and mCRPC who Previously Received Taxane-Based Chemotherapy…	0	Closed 3/2020	UWash
c19-231 (UW18051)	eFT508: A Phase 2… Study Examining the Effect of eFT508 in Patients with Advanced Castrate-resistant Prostate Cancer (CRPC)	3	Closed 3/2019	DFCI UWash
c19-248 (UW18002)	A Phase I… Study of PF-06821497 in the Treatment of Adult Patients with… Castration Resistant Prostate Cancer (CRPC)…	13	Open	UWash
c20-259 (RG1004978)	A Phase 1, First-in-Human, Dose Escalation Study of JNJ-63898081 in Subjects with Advanced Stage Solid Tumors	10	Closed 1/2022	UWash
c21-274 (RG1005474)	A…phase 2 study… of I-131-1095 Radiotherapy in combination with enzalutamide in mCRPC patients Who are 18F-DCFPyL prostate-specific membrane antigen (PSMA)-avid… (ARROW)	11	Closed 6/2022	UWash
c21-275 (RG1007001)	Durvalumab (MEDI4736) and Olaparib (AZD2281) for treatment of biochemically recurrent prostate cancer in men predicted to have a high neoantigen load: a pilot study	2	Open	UWash
c21-295 (RG1007001)	A Phase 1/Phase 2 Trial… of VTP-850 Prostate Cancer Immunotherapeutic in Men with Biochemical Recurrence after Definitive Local Therapy for Prostate Cancer	0	Start-up	UWash Columbia
c22-297 (RG1122235)	A Phase 1 Study of JNJ-78278343, a T-Cell-Redirecting Agent Targeting Human Kallikrein 2 (KLK2), for Advanced Prostate Cancer	0	Start-up	UWash Columbia
c22-303 (RG1122292)	A Phase 2 Trial of SRF617 in Combination With AB928 (Etrumadenant) and AB122 (Zimberelimab) in Patients With Metastatic Castration-Resistant Prostate Cancer	1	Open	UWash
	Total Therapeutic accruals:	***93***		

PCCTC# (UW#)	Trial Title	UWash Accrual	Status	Lead Site
c16-170 (CC9853)	Prostate Cancer Outcomes: An International Registry to Improve Outcomes in Men with Advanced Prostate Cancer (IRONMAN)	58	Open	Duke MSKCC DFCI
c19-235 (RG1006494)	PROMISE: A Prostate Cancer Registry of Outcomes and Germline Mutations for Improved Survival and Treatment Effectiveness		Open	UWash JHU
c20-258 (RG1006011)	The impact of DNA repair pathway alterations identified by circulating tumor DNA on sensitivity to Radium-223 in bone metastatic castration-resistant prostate cancer	15	Open	UWash
c21-271 (RG1006494)	Darolutamide Observational Study in non-metastatic castration-resistant prostate cancer patients	5	Open	UWash
	Total non-therapeutic accruals			

Appendix 2

Copies of original journal articles

787PD Prognostic associations of prostate-specific antigen (PSA) decline with survival, radiographic response and progression in chemotherapy-naïve men with metastatic castration-resistant prostate cancer (mCRPC) treated with enzalutamide

A.J. Armstrong[1], P. Lin[2], C.S. Higano[3], P. Iversen[4], C.N. Sternberg[5], B. Tombal[6], D. Phung[7], T. Parli[8], A. Krivoshik[9], T.M. Beer[10]

[1]Divisions of Medical Oncology and Urology, Duke Cancer Institute, Durham, NC, USA, [2]Biometrics, Medivation, Inc., San Francisco, CA, USA, [3]Medicine and Urology, University of Washington Seattle Cancer Care Alliance, Seattle, WA, USA, [4]Urology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark, [5]Department of Oncology, San Camillo and Forlanini Hospitals, Rome, Italy, [6]Urology, Cliniques Universitaires St. Luc, Brussels, Belgium, [7]Biostatistics, Astellas Pharma Europe B.V., Leiden, Netherlands, [8]Clinical Development, Medivation, Inc., San Francisco, CA, USA, [9]Medical Sciences - Oncology, Astella Pharma, Inc., Northbrook, IL, USA, [10]Oregon Health & Science University, OHSU Knight Cancer Institute, Portland, OR, USA

Background: In the PREVAIL clinical trial, enzalutamide provided significant improvements vs placebo in radiographic progression-free survival (rPFS) and overall survival (OS) in chemotherapy-naïve men with mCRPC. This post hoc analysis aimed to evaluate the prognostic association between the magnitude of PSA decline from baseline and clinical outcomes in PREVAIL.

Methods: Men from the enzalutamide and placebo arms of PREVAIL were grouped into categories of confirmed maximal PSA decline from baseline at month 3 of

Table: 787PD

Outcome	Maximal PSA Decline From Baseline at Month 3 in the Enzalutamide Arm (N = 872)			
	No Decline/ Decline < 30% (n = 94/872)	**≥ 30% Decline (n = 701/872)**	**≥ 50% Decline (n = 639/872)**	**≥ 90% Decline (n = 307/872)**
Best objective soft-tissue response (CR or PR), % (95% CI)	12.0 (4.5-24.3)	70.6 (65.1-75.6)	74.8 (69.2-79.9)	89.7 (82.8-95.0)
Median (95% CI) time to PSA progression, mo	3.7 (3.7-4.6)	13.8 (11.3-14.0)	13.9 (13.8-16.6)	22.5 (16.8-NYR)
Median (95% CI) rPFS, mo	7.9 (3.7-NYR)	NYR (13.8-NYR)	NYR (13.8-NYR)	NYR (13.8-NYR)
HR (95% CI) for rPFS	1.0 (ref)	0.20 (0.13-0.31)	0.17 (0.11-0.27)	0.10 (0.05-0.19)
Median (95% CI) OS, mo	23.1 (17.8-28.0)	32.4 (31.5-NYR)	NYR (31.5-NYR)	NYR (NYR-NYR)
HR (95% CI) for OS	1.0 (ref)	0.31 (0.22-0.42)	0.28 (0.20-0.39)	0.19 (0.12-0.28)

Abbreviations: CI, confidence interval; CR, complete response; HR, hazard ratio; mo, months; NYR, not yet reached; OS, overall survival; PR, partial response; PSA, prostate-specific antigen; ref, reference, rPFS, radiographic progression-free survival.

treatment: no decline/decline < 30% and ≥ 30%, ≥ 50% or ≥ 90% decline. Confirmation required PSA decline on ≥ 1 consecutive visit after month 3. Best overall soft-tissue response (per RECIST v1.1) was determined for patients with measurable disease at baseline (data cutoff: 16 Sep 2013). Time to PSA progression (data cutoff: 16 Sep 2013), rPFS (per PCWG2; data cutoff: 6 May 2012) and OS (data cutoff: 16 Sep 2013) were estimated using the Kaplan-Meier method.

Results: In PREVAIL, men were randomized to enzalutamide (n = 872) or placebo (n = 845). Most men in the placebo arm (66%, 558/845) had no PSA decline/decline < 30%, in contrast to 11% (94/872) in the enzalutamide arm. In the enzalutamide arm, 81% (701/872) of men had a PSA decline of ≥ 30% from baseline at week 13, 73% (639/872) had a PSA decline of ≥ 50% and 35% (307/872) had a PSA decline of ≥ 90%. Key outcomes for the enzalutamide arm are provided by PSA decline category in the Table. PSA flare (rise followed by a fall) after 3 months was rare with enzalutamide (< 1%).

Conclusions: PSA declines after 3 months of enzalutamide therapy are strongly associated with soft-tissue response and improvements in rPFS and OS. Providing updated prognostic information to chemotherapy-naïve men with mCRPC can be of clinical value given the heterogeneity of long-term outcomes.

Clinical trial identification: NCT01212991

Legal entity responsible for the study: This study was sponsored by Medivation, Inc. (which was was acquired by Pfizer, Inc. in September 2016) and Astellas Pharma, Inc., the co-developers of enzalutamide.

Funding: This study was sponsored by Medivation, Inc., (which was acquired by Pfizer, Inc. in September 2016) and Astellas Pharma, Inc., the co-developers of enzalutamide.

Disclosure: A.J. Armstrong: Consultant: Bayer, Sanofi, Novartis, Dendreon, Medivation, Janssen Biotech, Eisai Bureau: Dendreon, Sanofi, Medivation, Janssen Biotech Grant/Patent (inst) Dendron, Sanofi, Bayer, Pfizer, Novartis, BMS, Janssen Oncology, Medivation, Astellas, Gilead. P. Lin, T. Parli: Employment: Pfizer, Inc. C.S. Higano: Consulting/Travel: Dendreon, Bayer, Medivation, Ferring, J&J, AbbVie, Genentech, Pfizer, BHR, Orion, Sanofi, Amgen, Ockham, Teva, Astellas. P. Iversen: Consultant/Advisor, Meeting Participant/Lecturer, Scientific Study/Trial and Clinical Research Collaboration: Astellas Pharma, Medivation. C.N. Sternberg: Honoraria: Pfizer, Bristol-Myers Squibb, Novartis, Janssen, Bayer, Astellas Pharma, Sanofi, Eisai, Ipsen, GlaxoSmithKline, MSD. B. Tombal: Consulting: Astella, Bayer, Ferring, Janssen, Takeda, Steba Biotech, Sanofi Speakers Bureau: Amgen, Janssen Travel/Honoraria: Amgen, Astellas, Bayer, Ferring, Janssen, Sanofi. D. Phung: Employment: Astellas Pharma. A. Krivoshik: Employment and Travel/Expenses: Astellas Pharma Stock/Ownership Interests: Abbott Laboratories, AbbVie. T.M. Beer: Consulting: Astellas, Bayer, Dendreon, Janssen Japan, Novartis, AstraZeneca, Churchill, Proacta Stock/Ownership: Salarius.

Hepatic effects assessed by review of safety data in enzalutamide castration-resistant prostate cancer (CRPC) trials.

Presented Thursday, February 8, 2018

Authors:
Tomasz M. Beer, Simon Chowdhury, Fred Saad, Neal D. Shore, Celestia S. Higano, Peter Iversen, Karim Fizazi, Kurt Miller, Axel Heidenreich, Choung Soo Kim, De Phung, Jeffrey Kent Barrus, Natalia Nikolayeva, Andrew Krivoshik, Javier Waksman, Bertrand F. Tombal; Knight Cancer Institute, Oregon Health & Science University, Portland, OR; Guy's and St Thomas' Hospital NHS Foundation Trust, London, United Kingdom; Centre Hospitalier de l'Université de Montréal/CRCHUM, Montreal, QC, Canada; Carolina Urologic Research Center, Myrtle Beach, SC; University of Washington and Fred Hutchinson Cancer Research Center, Seattle, WA; University of Copenhagen, Rigshospitalet, Copenhagen, Denmark; Institut Gustave Roussy, University of Paris Sud, Paris, France; Charité Campus Benjamin Franklin, Berlin, Germany; Cologne University, Cologne, Germany; University of Ulsan College of Medicine/ Asan Medical Center, Seoul, Korea, Republic of (South); Astellas Pharma Inc., Leiden, Netherlands; Astellas Pharma Inc., Northbrook, IL; Pfizer Inc., San Francisco, CA; Cliniques Universitaires Saint-Luc, Brussels, Belgium

View Less

Abstract Disclosures

Background:
Androgen receptor inhibitor enzalutamide (ENZA) improves survival in patients with metastatic CRPC. As the liver is the main route of ENZA elimination, this post hoc analysis evaluated the hepatic effects of ENZA versus comparators in controlled CRPC trials.

Methods:
Safety data from two large Phase 3, placebo (PBO)- (PREVAIL, NCT0121299; AFFIRM, NCT00974311) and two smaller Phase 2, bicalutamide (BIC)-controlled (STRIVE, NCT01664923; TERRAIN, NCT01288911) ENZA trials in men with CRPC were assessed for hepatic impairment-related adverse events (AEs) using the following standardized narrow MedDRA queries V19.1: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; hepatitis, non-infectious; and liver-related investigation, signs, and symptoms. Liver-related laboratory test results were also evaluated. Data were summarized as follows: patients receiving ENZA in Phase 3 trials (n = 1671); patients receiving ENZA in Phase 2 trials (n = 380); patients receiving PBO (n = 1243); patients receiving BIC (n = 387); and combined ENZA-treated patients (n = 2051).

Results:
Percentages of hepatic impairment-related AEs ranged between 2.9% and 4.5% with ENZA, and were 2.7% with PBO and 5.4% with BIC (Table). The most common hepatic impairment-related AEs were increased aspartate (AST) and alanine aminotransferase (ALT; Table). Within each trial, the incidences of grade ≥3 AEs were similar, and dose reductions or discontinuations due to hepatic impairment-related AEs were low (Table). When adjusted for treatment exposure, AEs per 100 patient-years were lower with ENZA versus either PBO or BIC (Table).

Conclusions:
This combined analysis of CRPC trials demonstrates no hepatic safety signal with ENZA and thus routine liver tests are not required. Clinical trial information: NCT0121299; NCT00974311; NCT01664923; NCT01288911.

Potential hepatic impairment-related AE*	Phase 3 ENZA (n = 1671)	Phase 2 ENZA (n = 380)	Combined ENZA (n = 2051)	PBO (n = 1243)	BIC (n = 387)
Any AE	2.9	4.5	3.2	2.7	5.4
AST increased	0.9	0.8	0.9	1.0	1.8
ALT increased	0.7	1.3	0.8	0.6	1.3
Any grade ≥3	0.9	1.1	0.9	0.8	0.5
Leading to treatment discontinuation	0.2	0.3	0.2	0.2	0.3
Leading to dose reduction	< 0.1	0	< 0.1	0.2	0
AE rates per 100 patient-years	3.7	5.4	4.0	6.4	8.6

*Results all in %

ASCO Meeting Library

Clinical outcome of patients with germline DNA repair mutations: Results from a retrospective international study.

Presented Thursday, February 8, 2018

Authors:
Joaquin Mateo, Heather H. Cheng, Himisha Beltran, David Dolling, Wen Xu, Colin Pritchard, Helen Mossop, Pasquale Rescigno, Raquel Perez-Lopez, Verena Sailer, Michael Paul Kolinsky, Ada Balasopoulou, Claudia Bertan, Suzanne Carreira, Heather Thorne, Robert B. Montgomery, Shahneen Kaur Sandhu, Mark A. Rubin, Peter Nelson, Johann S. De Bono; Institute of Cancer Research and The Royal Marsden Hospital, London, United Kingdom; University of Washington, Seattle, WA; Weill Cornell Medical College, New York, NY; Institute of Cancer Research, London, United Kingdom; Princess Alexandra Hospital, Moorooka, Queensland, Australia; Institute of Cancer Research and The Royal Marsden NHS Trust Foundation, Sutton, United Kingdom; Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom; Weill Cornell Medicine, New York, NY; Peter MacCallum Cancer Centre, Melbourne, Australia; University of Washington Oncology, Seattle, WA; Peter MacCallum Cancer Centre, Victorian Comprehensive Cancer Centre, Melbourne, Australia; Fred Hutchinson Cancer Research Center, Seattle, WA

View Less

Abstract Disclosures

Background:
CRPC is enriched for germline mutations in DNA damage repair genes (gDDRm). BRCA2 mutations (g*BRCA2*m) associate with poor prognosis from localized PC, but prognostic and predictive value for standard therapy in CRPC is unclear. We reviewed clinical outcome of 390 patients previously tested for gDDRm.

Methods:

Patient records were reviewed for 372 patients from 3 institutions (Royal Marsden UK, Weill-Cornell NY, University of Washington, WA) with gDDRm status previously published (Pritchard et al, NEJM 2016) and 18 g*BRCA1/2*m carriers from KConFab consortium (Australia). Baseline characteristics and survival were annotated. Response (PSA50%/RECIST) and PFS (RECIST/PSA progression or start of a new therapy due to clinical progression) were collected for Abiraterone, Enzalutamide and Docetaxel. To account for potential differences between cohorts, a mixed effect model (Weibull distribution) with random intercept per cohort was pursued.

Results:

dDDRm status was available for n = 390 (60 gDDRm+, including 37 g*BRCA2*m, and 330 gDDRm-). Overall, 74% and 69% received Docetaxel and Abiraterone/Enzalutamide respectively; 47% gDDRm+ and 34% gDDRm- received PARPi and/or platinum. Median overall survival from CRPC was 3.0 vs 3.2 years in gDDRm+ vs gDDRm- (p = 0.73; g*BRCA2*m = 3.0 years, p = 0.72). Age and Gleason score at diagnosis were associated with survival from castration-resistance in multivariate analysis. Median PFS on Docetaxel for gDDRm+ (6.8 months; 6.3 for g*BRCA2*m) and gDDRm- (5.1 months) were not significantly different (p = 0.2). Similarly, RR to Docetaxel was similar for the two groups (61% vs 54% in gDDRm+ vs gDDRm-; 63% g*BRCA2*m). Median PFS and RR on first Abiraterone/Enzalutamide were similar across groups (PFS: 8.3 months gDDRm+, 8.3 months for gDDRm-; p = 0.9; RR 46% vs 56% respectively) The Interaction of PARPi/platinum therapy among gDDRm+ patients resulted in an aHR for OS from CRPC of 0.59 (95%CI 0.28-1.25; p = 0.17).

Print

Conclusions:

In this retrospective analysis, CRPC patients with gDDRm still benefited from standard therapies similarly to non-mutation carriers; interpretation of survival data should consider the high proportion treated with PARPi/platinum.

ASCO® Meeting Library

Results of a phase II trial of neoadjuvant abiraterone + prednisone+ enzalutamide + leuprolide (APEL) versus enzalutamide + leuprolide (EL) for patients with high-risk localized prostate cancer (PC) undergoing radical prostatectomy (RP).

Presented Thursday, February 8, 2018

Authors:
Rana R. McKay, Wanling Xie, Rosina Lis, Huihui Ye, Zhenwei Zhang, Quoc-Dien Trinh, Steven Lee Chang, Lauren Christine Harshman, Ashley Ross, Kenneth J. Pienta, Daniel W. Lin, William J Ellis, Robert B. Montgomery, Peter Chang, Andrew Wagner, Glenn Bubley, Adam S. Kibel, Mary-Ellen Taplin; Dana-Farber Cancer Institute, Boston, MA; Beth Israel Deaconess Medical Center, Boston, MA; Brigham and Women's Hospital/ Harvard Medical School, Boston, MA; Brigham and Women's Hospital, Boston, MA; Stanford University School of Medicine, Stanford, CA; Johns Hopkins Medicine, Baltimore, MD; James Buchanan Brady Urological Institute, Johns Hopkins University School of Medicine, Baltimore, MD; University Print Washington, Seattle, WA; University of Washington Oncology, Seattle, WA; Brigham and Women's Hospital/ Dana-Farber Cancer Center, Boston, MA

View Less

Abstract Disclosures

Background:
Patients with high-risk PC have an increased risk of recurrence and mortality despite therapy. Abiraterone, a CYP17 inhibitor, and enzalutamide, a next generation anti-androgen, have demonstrated improved overall survival in metastatic PC. In this multicenter randomized phase II trial, we evaluate the impact of second generation hormone therapy on RP pathologic outcomes.

Methods:
Eligible patients had biopsy Gleason score ≥4+3=7, PSA >20 ng/mL or cT3 disease (by prostate MRI). Lymph node were require to be <20 mm. Patients were randomized 2:1 to APE:EL for 6 cycles (24 weeks) followed by RP. All RPs underwent central pathology review. The primary endpoint was the rate of pathologic complete response (pCR) or minimum residual disease (MRD, tumor ≤5 mm). Secondary endpoints include PSA response, surgical staging at RP, positive margin rate, and safety.

Results:

75 patients were enrolled at four sites: DFCI/BWH (n=55), BIDMC (n=11), UW (n=5), JHU (n=4). Median age was 62 years. Most patients had NCCN high-risk disease [n=66, 88%; cT3 n=21 (28%), Gleason 8-10 n=59 (79%), PSA >20 ng/mL n=17 (23%)]. All patients completed 6 cycles followed by RP. Median PSA nadir was 0.03 and 0.02 ng/mL and time to nadir was 3.7 and 4.6 months in the APEL and EL arms, respectively. The combined pCR or MRD rate was 30% (n=15/50) in the APEL arm and 16% (n=4/25) in the EL arm. The response difference was 14% (80% CI -3%-30%, p=0.263). 15 patients (14 in APEL; 1 in EL) had grade 3 adverse events (AEs). The most common grade 3 AEs were hypertension (n=7) and ALT increase (n=5). No grade 4-5 AEs occurred.

Conclusions:

Neoadjuvant hormone therapy plus RP in men with high-risk PC resulted in favorable pathologic responses (≤5 mm residual tumor) in 16-30% with a trend towards improved pathologic outcomes with APEL and acceptable safety profile. Follow-up is necessary to evaluate the impact of therapy on recurrence rates. Clinical trial information: NCT02268175

Pathologic outcomes at RP.

	APEL (n=50)	EL (n=25)	Total (n=75)
pT2	38%	36%	37%
pT3	50%	56%	52%
+ Margins	18%	12%	16%
+ Seminal Vesicles	18%	28%	21%
+ Lymph Nodes	10%	12%	11%
pCR	12%	8%	11%
MRD	18%	8%	15%

Print

ASCO® Meeting Library

Proportion of biochemically-recurrent prostate cancer patients with durable undetectable PSA after short-course androgen deprivation therapy.

Presented Thursday, February 8, 2018

Authors:
Daniel M. Lim, Roman Gulati, Serge Aleshin-Guendel, Heather H. Cheng, Agnes M. Gawne, Jonathan T. Wingate, Ruth Douglas Etzioni, Evan Y. Yu; University of Washington, Seattle, WA; Fred Hutchinson Cancer Research Center, Seattle, WA; U.S. Army, Tacoma, WA, US

Abstract Disclosures

Print

Background:
Optimal utilization of novel therapies for advanced prostate cancer is challenging without a validated surrogate efficacy endpoint. Ongoing trials are using durable undetectable prostate specific antigen (PSA) levels as a marker of efficacy. The proportion of patients and clinical relevance of those with a prolonged undetectable PSA after a short course of androgen deprivation therapy (ADT) is uncertain.

Methods:
The University of Washington Caisis database was queried for radical prostatectomy patients who received 6–12 months of ADT after biochemical recurrence (BCR), defined as PSA ≥ 0.2 ng/mL and no radiographically detectable metastasis. Proportions of patients with undetectable PSA 12 and 24 months after ending ADT were compared to a hypothesized 5% rate using exact binomial tests. Associations with patient and tumor characteristics were examined using logistic regression, and associations with risk of subsequent metastasis and death from any cause were evaluated by log-rank tests.

Results:
After ineligibility exclusions, data were abstracted from 93 patients. Proportions of patients with undetectable PSA 12 and 24 months after ending ADT were n=23/93 (24.7%; 95% CI 16.4–34.8%; P<0.001) and n=14/93 (15.1%; 95% CI 8.5–24.0%; P<0.001), respectively. Proportions of patients with undetectable

PSA 12 and 24 months after testosterone recovery ≥ 50 ng/dL were n=16/65 (24.6%; 95% CI 14.8-36.9%) and n=10/65 (15.4%; 95% CI 7.6-26.5%), respectively. Being 1 year older at diagnosis was associated with an 11.5% (95% CI 3.1–21.9%; P=0.01) increase in the odds of having a detectable PSA after controlling for PSA at diagnosis, Gleason sum and time from initial therapy to BCR. Detectable PSA was associated with increased risk of metastasis (P=0.006) with marginal evidence of association with death from any cause (P=0.07).

Conclusions:

This single-institution retrospective analysis shows that it is not uncommon to have undetectable PSA 12 or 24 months after a short course of ADT. Additional analysis is needed to demonstrate the clinical value of this measure as a surrogate for prostate cancer outcomes and for consideration as a trial endpoint.

ASCO Meeting Library

Association of undetectable PSA with time to metastasis and survival after short-course androgen deprivation therapy for biochemically-recurrent prostate cancer patients.

Authors:
Evan Y. Yu, Roman Gulati, Serge Aleshin-Guendel, Heather H. Cheng, Agnes M. Gawne, Jonathan T. Wingate, Ruth Douglas Etzioni, Daniel M. Lim; Seattle Cancer Care Alliance, Seattle, WA; Fred Hutchinson Cancer Research Center, Seattle, WA; University of Washington, Seattle, WA; U.S. Army, Tacoma, WA, US

Abstract Disclosures

Background:
Optimal utilization of novel therapies for advanced prostate cancer is challenging without a validated surrogate efficacy endpoint. Durable undetectable prostate-specific antigen (PSA) levels are being used in ongoing trials as a marker of efficacy. The clinical relevance of patients with a prolonged undetectable PSA after short course androgen deprivation therapy (ADT) is uncertain.

Methods:
The University of Washington Caisis database was queried for radical prostatectomy patients who received 6–12 months of ADT after biochemical recurrence (BCR), defined as PSA ≥0.2 ng/mL and no radiographically detectable metastasis. Proportions of patients with undetectable PSA 12 and 24 months after ending ADT were compared to a hypothesized 5% rate using exact binomial tests. Associations with patient and tumor characteristics were examined using logistic regression, and associations with risk of subsequent metastasis and death were evaluated by log-rank tests.

Results:
After ineligibility exclusions, 23/93 (24.7%; 95% CI 16.4–34.8%; P < 0.001) and 14/93 (15.1%; 95% CI 8.5–24.0%; P < 0.001) of patients had undetectable PSA 12 and 24 months after ending ADT, respectively. Being 1 year older at diagnosis was associated with a 14% (95% CI 5.1–23.7%; P = 0.006) decrease in the odds of detectable PSA after controlling for PSA at diagnosis, PSA doubling time, Gleason sum and time from initial therapy to BCR. Detectable PSA at 12 months was associated with increased risk of metastasis (P = 0.006), prostate cancer-specific death (P = 0.028) and death from any cause (P = 0.065).

Conclusions:

This single-institution retrospective analysis shows that it is not uncommon to have undetectable PSA 12 or 24 months after a short course of ADT, and this finding correlates with lower risk of metastasis and prostate cancer-specific death. No baseline prognostic characteristic other than age was associated with a durable undetectable PSA. Because of association with lower risks of metastasis and prostate cancer-specific death, it may be reasonable to consider undetectable PSA as a clinical trial endpoint.

ASCO® Meeting Library

Evaluation of an immunotherapeutic DNA-vaccine in biochemically relapsed prostate cancer.

Presented Saturday, June 2, 2018

Authors:
Neal D. Shore, Elisabeth I. Heath, Luke T. Nordquist, Heather H. Cheng, Kamalnayan Bhatt, Matthew Morrow, Trevor McMullan, Kimberly Kraynyak, Jessica Lee, Brian Sacchetta, Li Liu, Samantha Rosencranz, Scott T. Tagawa, Rahul Atul Parikh, Ronald F Tutrone, Jorge A. Garcia, Young E. Whang, William Kevin Kelly, Ildiko Csiki, Mark L. Bagarazzi; Carolina Urologic Research Center, Myrtle Beach, SC; Barbara Ann Karmanos Cancer Institute, Wayne State University, Detroit, MI; Urology Cancer Center and GU Research Network, Omaha, NE; University of Washington, Seattle, WA; Inovio Pharmaceuticals, Inc., Plymouth, PA; Inovio Pharmaceuticals, Plymouth Meeting, PA; Inovio Pharmaceuticals, Inc., Collegeville, PA; Inovio Pharmaceuticals, Inc., Blue Bell, PA; Sandra and Edward Meyer Cancer Center, New York, NY; University of Kansas, Kansas City, KS; Chesapeake Urology, Towson, MD; Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; University of North Carolina at Chapel Hill, Chapel Hill, NC; Sidney Kimmel Cancer Center at Thomas Jefferson University, Philadelphia, PA; Inovio Pharmaceuticals, Plymouth Meeting, PA, US

View Less

Abstract Disclosures

Background:
The DNA immunotherapy, INO-5150 (PSA and PSMA) +/- INO-9012 (IL-12) was assessed for safety, immunogenicity and the effect on PSA kinetics in biochemically recurrent prostate cancer patients (pts).

Methods:
Phase I, open-label, multi-center study included pts with rising PSA after surgery and/or RT, PSA doubling time (PSADT) > 3 months (mos), testosterone > 150 ng/dL, no concurrent ADT and no evidence of metastases by conventional imaging. Safety, immunogenicity and efficacy were evaluated in 4 treatment arms in 60 planned pts (A: 16, 2mg INO-5150; B: 15, 8.5 mg INO-5150; C: 15, 2mg INO-5150+1mg INO-9012; D: 16, 8.5mg INO-5150+1mg INO-9012). Pts received 4 IM doses of vaccine followed by electroporation on day 0, wks 3, 12 and 24 and followed for 72 wks.

Results:

The study has concluded and 50/62 (80%) pts completed all visits. 90% of pts had Grade (Gr) 1-3 AEs, primarily injection site reactions which were Gr 1. Across 4 cohorts, 47/61 (77%) of all evaluable pts demonstrated immunogenicity, [35/58 (60%) had IFN-γ reactivity by ELISPOT, 6/61 (10%) and 5/61 (8%) had antibody titers against PSA and PSMA, respectively, and 19/50 (38%) had CD38, Perforin+CD8 T cell responses]. Pts (38%) with CD38 and Perforin + CD8 T cell immune reactivity had attenuated % PSA rise compared to non-reactive pts ($p = 0.05$, $n = 50$). Pts with no known progression during the study showed significant differences in log_2PSA change and PSADT pre-treatment baseline (D0) vs wk 27 (post-immunotherapy time point, $n = 34$, $p < 0.0001$) or wk 72 (end of follow-up, $n = 27$, $p < 0.0001$). Furthermore, pts with D0 PSADT≤ 6 mos and no known progression during the study showed significant differences in log_2PSA change and PSADT in D0 vs wk 27 ($n = 15$, $p < 0.0001$) or wk 72 ($n = 10$, $p = 0.002$).

Conclusions:

INO-5150 +/- INO-9012 was safe, well tolerated and immunogenic. A clinical effect was demonstrated by evidence of dampening % rise in PSA and increased PSADT in the majority of patients. In patients with no known disease progression during the study, a significant PSA stabilizing effect of the immunotherapy was observed. Additional analyses are ongoing to further elucidate the correlation of immunologic efficacy and clinical benefit. Clinical trial information: NCT02514213

ASCO Meeting Library

c15-148: Phase I/II trial of concurrent chemohormonal therapy using enzalutamide and cabazitaxel in patients with metastatic castration resistant prostate cancer (mCRPC).

Presented Saturday, June 2, 2018

Authors:
Julie Nicole Graff, Tomasz M. Beer, Joshi J. Alumkal, Dustin Kreitner, Delia Petreaca, George V. Thomas, Heather H. Cheng; VA Portland Health Care System, Knight Cancer Institute, Oregon Health & Science University, Portland, OR; Knight Cancer Institute, Oregon Health & Science University, Portland, OR; OHSU Knight Cancer Institute, Portland, OR; University of Washington, Seattle, WA

Abstract Disclosures

Print

Background:
The management of mCRPC has been both enhanced and complicated by the rapid emergence of at least five new agents that can lengthen survival. While great strides have been made in developing new agents for mCRPC, response rates and duration have remained modest, and men ultimately succumb to their disease. Historically, combined chemo-hormonal therapy has not improved outcomes for patients with prostate cancer, but earlier trials were hindered by lack of efficacious chemotherapy and weaker hormonal agents. In this study, we aim to determine if potential synergistic effects between two newer and more effective agents can be identified and exploited for therapeutic effect, and to obtain correlative biological information that may offer predictive and response value.

Methods:
An initial 3-12 study subjects will be treated with cabazitaxel at 25 mg/m^2 on day 1 and enzalutamide 160 mg daily every 21 days. These subjects will be permitted to continue on cabazitaxel and enzalutamide until progression and will be included in the final analysis of efficacy. The trial will proceed to phase II stage at the dose of 25 mg/m^2 if 0/3 or 1/6 patients receiving 25 mg/m^2 had DLT. The dose de-escalation will happen if ≥2/3 or ≥2/6 patients receiving 25 mg/m^2 had DLT. The trial will proceed to Phase II stage at the dose of 20 mg/m^2 if 0/3 or 1/6 patients receiving 20 mg/m^2 had DLT. In the absence of treatment delays due to adverse events, treatment with cabazitaxel and enzalutamide will continue for 6-10 cycles. Patients

may then continue enzalutamide monotherapy on a 28-day cycle until progression or limiting toxicity. For the phase I portion of this trial an initial 3 study subjects were treated with cabazitaxel at 25 mg/m^2 on day 1 and enzalutamide 160 mg daily every 21 days; no DLTs occurred. These subjects will be permitted to continue on cabazitaxel and enzalutamide until progression and will be included in the final analysis of efficacy. The phase II patients are treated with 25 mg/m2 cabazitaxel and 160 mg enzalutamide. The trial is open at 2 sites and managed by the Prostate Cancer Clinical Trials Consortium (PCCTC). Clinical trial information: NCT02522715

Print

ASCO Meeting Library

c15-160: Enzalutamide (ENZA) plus CC-115 in men with metastatic castration-resistant prostate cancer (mCRPC): A phase 1b Prostate Cancer Clinical Trials Consortium study.

Presented Saturday, June 2, 2018

Authors:
Dana E. Rathkopf, Karen A. Autio, Emmanuel S. Antonarakis, Heather H. Cheng, Gabrielle Arauz, Annelise Slack, Melanie Hullings, Howard I. Scher, Felix Y Feng, Karen E. Knudsen; Memorial Sloan Kettering Cancer Center, New York, NY; Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; University of Washington, Seattle, WA; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University; Memorial Sloan-Kettering Cancer Center, New York, NY; University of California San Francisco, San Francisco, CA; Sidney Kimmel Cancer Center at Thomas Jefferson University, Philadelphia, PA

View Less

Abstract Disclosures

Background:
Studies in PTEN-deficient prostate cancer (PC) models have shown additive anti-tumor activity when ENZA is combined with PI3K pathway inhibition due to modulation of reciprocal feedback loops. In addition, interplay between AR and DNA-PK regulates hormone-dependent DNA repair and PC progression. This phase Ib trial aims to optimize therapy for mCRPC with the combination of ENZA and the dual mTOR/DNA-PK inhibitor CC-115.

Methods:
This was a phase Ib multicenter trial (NCT02833883) for first-line mCRPC patients. Treatment was fixed dose ENZA (160 mg PO QD) with escalating doses of CC-115 (5 mg and 10 mg PO BID) using a 3 x 3 design. The primary endpoints were safety, PK and the recommended phase 2 dose (RP2D) of the combination. Secondary endpoints were PSA response, time on study and exploratory correlates using tumor biopsies, CTCs and ctDNA.

Results:

16 patients were treated: 9 in dose escalation and 7 in dose expansion, for a total of 13 patients treated at the RP2D of CC-115 10 mg PO BID. There were no drug-drug interactions. Median time on study was 26 (18-74+) weeks (wks), and 9 patients remain on active treatment. All evaluable patients had a > 50% PSA response, and 60% of patients achieved a ≥90% decline. The most common AEs were low grade fatigue (31%) and diarrhea (25%). At the RP2D, 8/13 (62%) patients developed rash: grade 3 (n = 6), grade 2 (n = 1) and grade 1 (n = 1) prompting dose reduction. 12 patients had baseline tissue analysis by IHC and/or NGS: 6 men had PTEN inactivation and 3 had DNA damage response and repair (DDR) alterations. Median time on study for those with PTEN deletions was 25 wks (7-57+), and was 29 wks (28-41+) for those with DDR alterations. Data on ctDNA and CTC biomarkers is pending.

Conclusions:

The combination of ENZA and CC-115 is safe and active in mCRPC, as demonstrated by all evaluable patients achieving a > 50% PSA decline and 60% achieving a ≥90% PSA decline. Due to a higher than expected incidence of rash, the protocol was amended to continue with CC-115 at 7.5 mg PO BID for the phase 2 expansion. Funding: Celgene and Gateway for Cancer Research. Clinical trial information: NCT02833883

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 28: 2264–2271, 2017
doi:10.1093/annonc/mdx283
Published online 15 June 2017

ORIGINAL ARTICLE

Androgen receptor mutations in patients with castration-resistant prostate cancer treated with apalutamide

D. E. Rathkopf[1*], M. R. Smith[2], C. J. Ryan[3], W. R. Berry[4], N. D. Shore[5], G. Liu[6], C. S. Higano[7], J. J. Alumkal[8], R. Hauke[9], R. F. Tutrone[10], M. Saleh[11], E. Chow Maneval[12†], S. Thomas[13], D. S. Ricci[13], M. K. Yu[14], C. J. de Boer[15], A. Trinh[14], T. Kheoh[16], R. Bandekar[13], H. I. Scher[1] & E. S. Antonarakis[17]

[1]Sidney Kimmel Center for Prostate and Urologic Cancers, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York; [2]Massachusetts General Hospital and Harvard Medical School, Boston; [3]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco; [4]Cancer Centers of North Carolina, Raleigh; [5]Carolina Urologic Research Center, Myrtle Beach; [6]University of Wisconsin Carbone Cancer Center, Madison; [7]University of Washington, Fred Hutchinson Cancer Research Center, Seattle; [8]Knight Cancer Institute, Oregon Health & Science University, Portland; [9]Nebraska Cancer Specialists, Omaha; [10]Chesapeake Urologic Research Associates, Baltimore; [11]University of Alabama Comprehensive Cancer Center, Birmingham; [12]Aragon Pharmaceuticals, San Diego; [13]Janssen Research & Development, Spring House; [14]Janssen Research & Development, Los Angeles; [15]Janssen Biologics, B. V., Leiden, the Netherlands; [16]Janssen Research & Development, San Diego; [17]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, USA

*Correspondence to: Dr Dana E. Rathkopf, Department of Medicine, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA. Tel: +1-646-422-4379; Fax: +1-212-988-0701; E-mail: rathkopd@mskcc.org

†Present address: Ignyta, Inc., San Diego, CA, USA

Background: Mutations in the androgen receptor (AR) ligand-binding domain (LBD), such as F877L and T878A, have been associated with resistance to next-generation AR-directed therapies. ARN-509-001 was a phase I/II study that evaluated apalutamide activity in castration-resistant prostate cancer (CRPC). Here, we evaluated the type and frequency of 11 relevant AR-LBD mutations in apalutamide-treated CRPC patients.

Patients and methods: Blood samples from men with nonmetastatic CRPC (nmCRPC) and metastatic CRPC (mCRPC) pre- or post-abiraterone acetate and prednisone (AAP) treatment (≥6 months' exposure) were evaluated at baseline and disease progression in trial ARN-509-001. Mutations were detected in circulating tumor DNA using a digital polymerase chain reaction-based method known as BEAMing (beads, emulsification, amplification and magnetics) (Sysmex Inostics' GmbH).

Results: Of the 97 total patients, 51 had nmCRPC, 25 had AAP-naïve mCRPC, and 21 had post-AAP mCRPC. Ninety-three were assessable for the mutation analysis at baseline and 82 of the 93 at progression. The overall frequency of detected AR mutations at baseline was 7/93 (7.5%) and at progression was 6/82 (7.3%). Three of the 82 (3.7%) mCRPC patients (2 AAP-naïve and 1 post-AAP) acquired *AR* F877L during apalutamide treatment. At baseline, 3 of the 93 (3.2%) post-AAP patients had detectable *AR* T878A, which was lost after apalutamide treatment in 1 patient who continued apalutamide treatment for 12 months.

Conclusions: The overall frequency of detected mutations at baseline (7.5%) and progression (7.3%) using the sensitive BEAMing assay was low, suggesting that, based on this assay, AR-LBD mutations such as F877L and T878A are not common contributors to *de novo* or acquired resistance to apalutamide.

ClinicalTrials.gov identifier: NCT01171898.

Key words: apalutamide, ARN-509, castration-resistant prostate cancer, androgen receptor, mutations

Introduction

Castration-resistant prostate cancer (CRPC) is the lethal form of the disease that carries a poor prognosis [1, 2]. Molecular profiling studies have shown that androgen receptor (AR) overexpression is associated with resistance to conventional antiandrogens, and pre-clinical experiments confirm that AR overexpression contributes

to CRPC progression [3]. This insight and the demonstration that androgen ligands persist in CRPC patient tumors despite medical castration led to the eventual clinical development of novel androgen-AR axis–signaling inhibitors, including most recently, apalutamide [4, 5].

Although the majority of patients respond to these next-generation AR-targeted agents, the durability of response is limited [6], and only a subset benefit from sequential AR-directed therapies [7–10]. Several potential mechanisms have been proposed to explain resistance to these agents, including DNA alterations in the AR gene, the production of AR mRNA splice variants such as AR-V7 [11, 12], increased mitogen-activated protein kinase signaling and alternative signaling pathways [3]. Point mutations in the AR ligand-binding domain (AR-LBD) have also been associated with resistance to AR-targeted therapy [13–20], including *AR* F877L and *AR* T878A (formerly *AR* F876L and *AR* T877A) [21], which have been associated with resistance to apalutamide, enzalutamide or the androgen biosynthesis inhibitor abiraterone acetate (hereafter abiraterone), respectively. Additionally, although all AR mutations alter the specificity of ligand binding, there are 2 types of AR mutations, those that convert AR antagonists to agonists (e.g. F877L, W742L/C) and those that result in broadened ligand specificity and a 'promiscuous AR' that can bind to other endogenous steroids [17].

To evaluate the relationship of AR-LBD mutations and resistance to next-generation antiandrogens, Balbas et al. [14] screened for human prostate cancer cell populations with persistent AR transcriptional activity, proliferative ability and tumorigenic potential in the presence of enzalutamide using an AR-regulated enhanced green fluorescent protein reporter and a randomly mutagenized AR library. These investigators identified a novel mutation, *AR* F877L, that spontaneously arose in cells with prolonged treatment with enzalutamide and apalutamide [14]. Joseph et al. [18] and Korpal et al. [19] confirmed these findings with *AR* F877L-expressing prostate cancer cell lines in castrated mice. Neither enzalutamide nor apalutamide inhibited tumor growth in the *AR* F877L-expressing tumors, but both drugs exhibited robust antitumor activity in wild-type AR-expressing tumors [18, 19]. Based on these preclinical data, Joseph et al. [18] used the BEAMing (beads, emulsification, amplification and magnetics) technique to evaluate serial circulating tumor DNA (ctDNA) samples from 29 patients with metastatic CRPC (mCRPC) treated on a phase I study of apalutamide. As expected, *AR* F877L was not found in pretreatment samples but the mutation was detected in 3 (10%) post-apalutamide patients with a rising prostate-specific antigen (PSA), suggesting a possible mechanism for acquired treatment resistance [18]. There is biochemical evidence based on engineered cell line models that enzalutamide is only a weak partial agonist of *AR* F877L, but a strong partial agonist of the double mutant *AR* F877L/T878A [22, 23].

The *AR* T878A mutation has been associated with resistance to abiraterone in a xenograft model [15], which was subsequently detected in metastatic tumor biopsies from CRPC patients relapsing on the CYP17A1 inhibitors abiraterone or ketoconazole [16]. In a recent study, men harboring the *AR* T878A mutation in ctDNA showed inferior PSA response rates and shorter overall survival with abiraterone compared with men with a wild-type AR gene [24]. These studies and others underscore the need to further investigate predictive biomarkers for resistance to AR-targeted therapies.

The aim of the present study was to evaluate the frequency of F877L, T878A and other AR-LBD mutations at baseline and disease progression in nonmetastatic (nm) and mCRPC patients who were abiraterone plus prednisone naïve (AAP-naïve) or who had previously received abiraterone plus prednisone (post-AAP) [25, 26]. Eleven somatic AR-LBD mutations were evaluated at baseline and disease progression in ctDNA using BEAMing, a digital polymerase chain reaction (PCR)-based method (supplementary Table S1, available at *Annals of Oncology* online).

Methods

Patients with nmCRPC and mCRPC were enrolled in a phase II trial of apalutamide (ARN-509-001) [25, 26]. All patients had pathologically confirmed prostate cancer, had been medically or surgically castrated (serum testosterone of $\leq$50 ng/dl) and had an Eastern Cooperative Oncology Group performance status of 0–1. Patients were excluded if they had received prior enzalutamide, ketoconazole or chemotherapy for mCRPC or had distant metastases with nmCRPC. Patients in the mCRPC cohort had disease progression based on either PSA progression ($\geq$2 ng/ml within 2 weeks of study enrollment) or radiographic progression ($\geq$2 new bone lesions, Prostate Cancer Working Group 2 criteria) [27] and had no prior exposure to abiraterone plus prednisone (i.e. AAP-naïve cohort) or received $\geq$6 months of abiraterone plus prednisone treatment before disease progression (i.e. post-AAP cohort).

Plasma samples were sent to Sysmex Inostics' GmbH (Hamburg, Germany) analytical facility on dry ice; samples were stored at –70 °C until they were analyzed. Samples were thawed at room temperature for 15–30 min before DNA preparation. BEAMing (Sysmex Inostics' GmbH), which combines emulsion PCR using magnetic beads coated with gene-specific primers to detect and quantify known mutations in ctDNA [28], was used to detect 11 possible somatic AR-LBD mutations in the patient samples (i.e. 11 of >30 known AR-LBD mutations available to assay via BEAMing at the time of the analysis) (supplementary Table S1, available at *Annals of Oncology* online). These 11 mutations affect 6 key amino acid residues (V716, W742, H875, F877, T878 and M896). Detection, quantification and validation are discussed in the supplementary methods, available at *Annals of Oncology* online).

Results

Baseline data ($N = 97$) were similar among cohorts, with the exception of percentage of black and Asian patients, baseline PSA and Gleason score (supplementary Table S2, available at *Annals of Oncology* online). Ninety-three of 97 (96%) patients in the phase II study were assessable for the AR mutation analysis at baseline (nmCRPC, $n = 50$; AAP-naïve mCRPC, $n = 24$; post-AAP mCRPC, $n = 19$); 82 of the 93 (88%) patients assessable at baseline were assessable for the mutation analysis at progression (nmCRPC, $n = 47$; AAP-naïve mCRPC, $n = 20$; post-AAP mCRPC, $n = 15$). The median (range) treatment duration was 26.9 (0.03–37.84) months for the nmCRPC cohort, 20.97 (2.63–37.54) months for the cohort with AAP-naïve mCRPC and 4.87 (1.28–23.2) months for those with post-AAP mCRPC. A low frequency of AR mutations was detected in the overall patient population (Table 1). *AR* F877L and *AR* T878A mutations were found in more than one patient, and these are the focus of this report.

Table 1. Summary of overall androgen receptor mutation status

AR point mutation[b]	Associated drug resistance	Baseline[a] *N* = 93 *n* (%)	Progression 'acquired' *N* = 82 *n* (%)	Total baseline and progression 'acquired' *N* = 93 *n* (%)
F877L[c]	Enzalutamide [14, 18, 19] Apalutamide [14, 18]	2 (2.2)	3 (3.7)	5 (5.4)
T878A[d]	Abiraterone [15, 16]	3 (3.2)	1 (1.2)	4 (4.3)
W742C[e]	Bicalutamide [17]	1 (1.1)	0	1 (1.1)
V716T	Flutamide [17]	0	1 (1.2)	1 (1.1)
H875Y	Flutamide [20] Abiraterone [13]	1 (1.1)	1 (1.2)	2 (2.2)

[a]Four nmCRPC patients were excluded from the efficacy analysis as they were later determined to have metastases on their screening scans.
[b]*AR* M896T and *AR* M896V were not detected.
[c]Three possible nucleotide changes (T → C, C → A and C → G).
[d]Two possible amino acid changes (T → A and T → S).
[e]Two possible amino acid changes (W → C and W → L).
AR, androgen receptor.

Table 2. Androgen receptor F877L and T878A mutation status[a] in individual patients treated with apalutamide in the nmCRPC, AAP-naïve and post-AAP cohorts

Cohort	Patient ID#	*AR* mutation[b]	Mutation fraction at baseline[c]	Cycle at which mutation fraction at progression detected	Mutation fraction at progression[d,e]	12-Week PSA change[f]	Treatment duration (months)[g]
nmCRPC	1	F877L	(0.02%)	8	(0.3%)	−92.2%	6.9
AAP-naïve	2	F877L	–	22	(0.721%)	−77.7%	24.9
	3	F877L	(0.032%)	11	(0.41%)	−66.9%	11.0
	4	F877L	–	9	(0.18%)	−97.3%	8.0
Post-AAP	5	F877L	–	4	(0.04%)	+55.9%	3.4
	6	T878A	(0.84%)	4	(5.46%)	+112.7%	2.8
	7	T878A	(0.07%)	14	–	−62.7%	12
	8	T878A	(1.96%)	6	(0.4%)	−90.1%	4.8
	9	T878A	–	10	(0.02%)	−80.8%	23.2

[a]A plasma sample was deemed positive for a given mutation if the percentage of mutant beads was above the cutoff (0.02%).
[b]No F877L/T878A double mutants were detected.
[c]Number of mutation positive patients at baseline (F877L, *n* = 2/93; T878A, *n* = 3/93).
[d]Number of mutation positive patients at progression (F877L, *n* = 5/82; T878A, *n* = 3/82).
[e]Disease progression on apalutamide was defined as evidence of both PSA progression (≥25% and >2 ng/ml above PSA nadir confirmed ≥3 weeks later or >2 ng/ml above baseline PSA after 12 weeks) and radiographic progression (soft tissue metastases by modified Response Evaluation Criteria In Solid Tumors 1.0) seen on computed tomography/magnetic resonance imaging scans and/or bone metastases by ^{99m}Tc-methylene diphosphate bone scans by Prostate Cancer Working Group 2 criteria, and clinically by the occurrence of a skeletal-related event, pain progression, or worsening of disease-related symptoms requiring new systemic anti-prostate cancer therapy.
[f]Median 12-week PSA change in F877L mutation negative patients (*n* = 86) was −79.8% (range, −99.9 to +175). Median 12-week PSA change in T878A mutation negative patients (*n* = 87) was −81.2% (range, −99.9 to +175).
[g]Median treatment duration in F877L mutation-negative patients (*n* = 92) was 19.6 months (range, 0.03–37.8). Median treatment duration in T878A mutation-negative patients (*n* = 93) was 18.4 months (range, 0.03–37.8).
–, undetected. AAP, abiraterone acetate plus prednisone; AR, androgen receptor; mCRPC, metastatic castration-resistant prostate cancer; PSA, prostate-specific antigen.

AR F877L

Two of the 93 (2.2%) patients harbored the *AR* F877L mutation at baseline at a mutation frequency of <0.05%, and both were subsequently found to have a PSA decline in response to apalutamide (Table 2; Figure 1A and B). One of these patients was in the nmCRPC cohort (12-week PSA change, –92.2%; treatment duration, 6.9 months) and the other was in the AAP-naïve cohort (12-week PSA change, –66.9%; treatment duration,

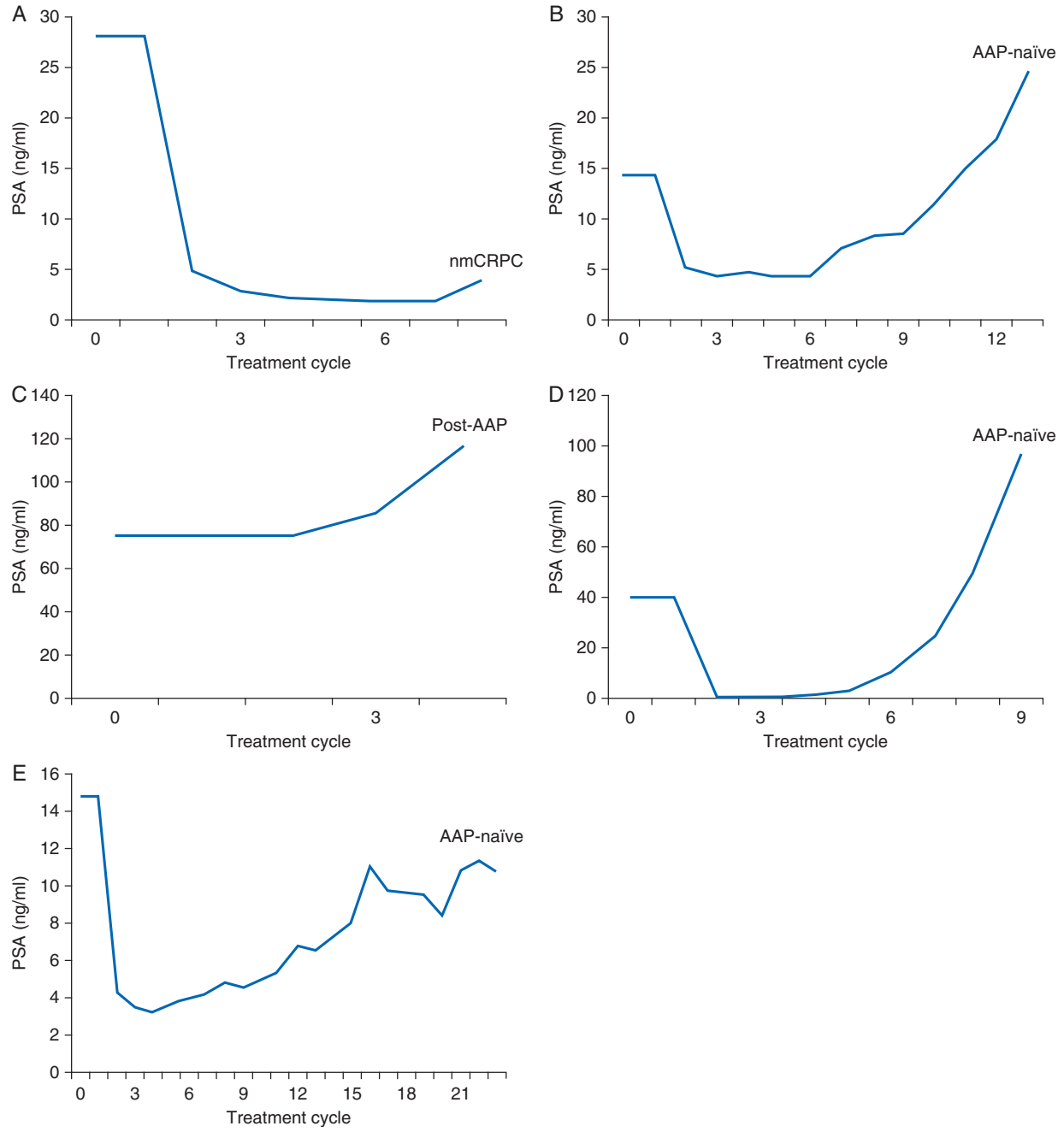


Figure 1. PSA changes in patients with androgen receptor F877L mutations detected at baseline [(A) Pt ID#1, (B) Pt ID#3] and at progression on apalutamide [(C) Pt ID#5, (D) Pt ID#4, (E) Pt ID#2]. AA, abiraterone acetate; PSA, prostate-specific antigen.

11.0 months). Both patients had detectable *AR* F877L and an increase in the mutation frequency at the time of progression.

Three additional patients [3/82 (3.7%)] were found to have the mutation at progression that had not been detected at baseline (Table 2); the PSA trajectory is shown in Figure 1C–E. The single patient in the post-AAP cohort who acquired *AR* F877L demonstrated no PSA decline (12-week PSA change, +55.9%; treatment duration, 3.4 months) and had a relatively low mutation frequency of 0.04% (Table 2; Figure 1C). The other 2 patients with acquired *AR* F877L were both in the AAP-naïve cohort with 12-week PSA changes of –97.3% and –77.7%, treatment durations of 8.0 and 24.9 months, respectively, and mutation frequencies of 0.18% and 0.72%, respectively (Table 2; Figure 1D and E, respectively).

AR T878A

Three of 93 (3.2%) patients had the *AR* T878A mutation at baseline (Table 2); all had previously received at least 6 months of abiraterone and demonstrated similar baseline characteristics.

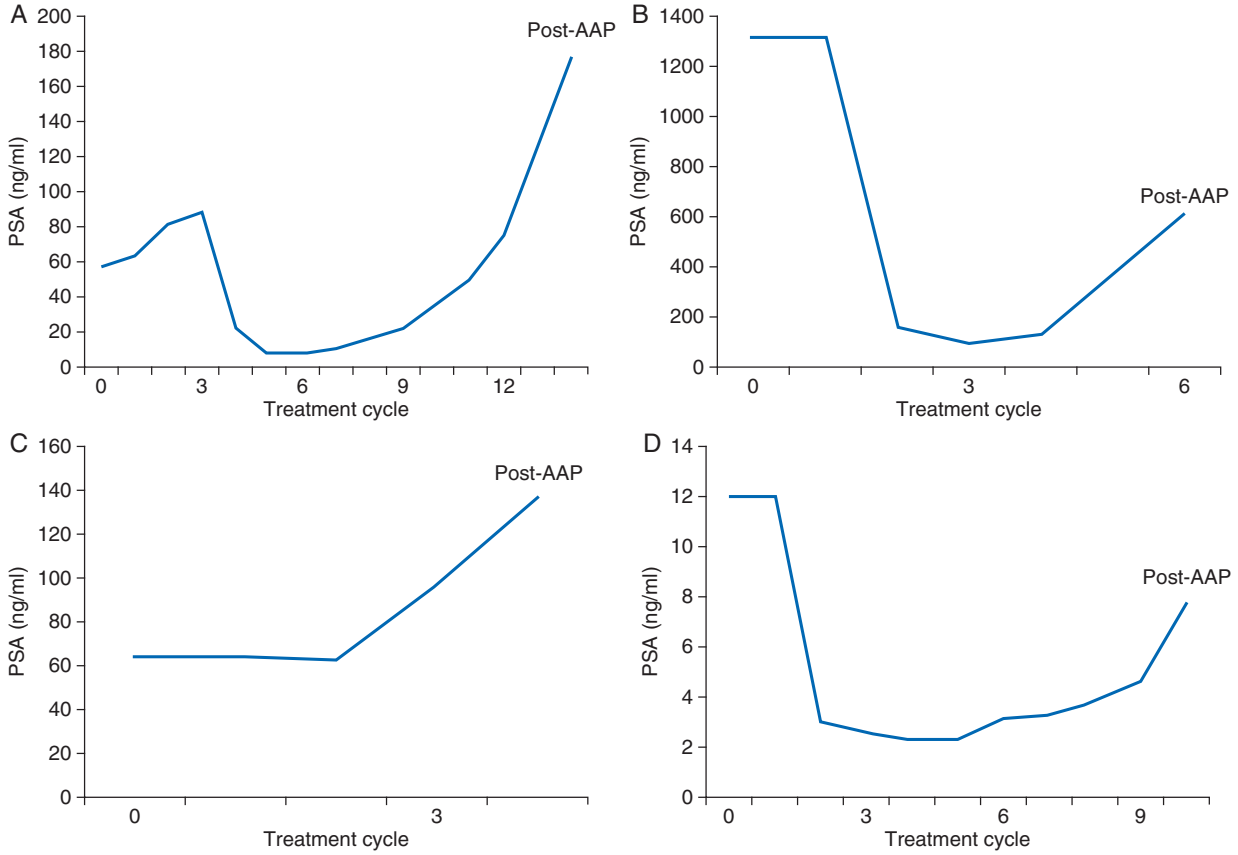


Figure 2. PSA changes in patients with androgen receptor T878A mutations detected at baseline [(A) Pt ID#7, (B) Pt ID#8, (C) Pt ID#6] and at progression on apalutamide [(D) Pt ID#9]. AA, abiraterone acetate; PSA, prostate-specific antigen. Baseline characteristics for these patients are shown in Table 3.

Two had a PSA decline while on treatment with apalutamide, including 1 who had lost the mutation by the time of progression on apalutamide (Figure 2A; Table 3) (12-week PSA change, −62.7%; treatment duration, 12.0 months), and a second who had a decreased mutation fraction from 1.96% at baseline to 0.4% at progression (Figure 2B; Table 3) (12-week PSA change, −90.1%; treatment duration, 4.8 months). The third patient had an increased mutation fraction from 0.84% at baseline to 5.46% at progression and had no PSA decline (12-week PSA change, +112.7%; treatment duration, 2.8 months) (Figure 2C; Table 3). The PSA kinetics increased for these patients after *AR* T878A detection at progression (Figure 2A–D). One post-AAP patient acquired the *AR* T878 mutation at progression at a relatively low frequency of 0.02%. This patient had a PSA decline in response to apalutamide (12-week PSA change, –80.8%; treatment duration, 23.2 months) (Figure 2D; Table 3).

Table 3. Baseline demographics and disease characteristics of post-AAP patients with T878A mutations at baseline corresponding to patients shown in Figure 2 (per Figure 2A–C) and progression on apalutamide (per Figure 2D)

Patient	A (Pt ID#7)	B (Pt ID#8)	C (Pt ID#6)	D (Pt ID#9)
Age	83	64	74	58
Race	White	White	White	White
Baseline PSA (ng/ml)	58.4	1315.2	64.1	12.0
ECOG PS	1	1	1	0
Gleason score	4+5	4+3	4+3	N/A

AAP, abiraterone acetate plus prednisone; ECOG PS, Eastern Cooperative Oncology Group performance status; PSA, prostate-specific antigen.

Discussion

The survival benefits seen with agents that target the AR-signaling pathway have transformed the management of mCRPC. Nevertheless, one-third of patients do not respond to second-generation AR-targeted therapies, and the majority of those who initially respond, will acquire resistance to these agents. The optimal treatment of these patients, and how best to sequence available life-prolonging therapies, have not been established due to the inability to identify patients most likely to respond (or not respond) to specific AR-targeted drugs. This demonstrates the need for predictive molecular biomarkers to better inform treatment selection [11, 12, 24, 29]. Here, we report results of ctDNA sequencing using the BEAMing assay on samples from a phase II study of apalutamide in 3 distinct cohorts

(nm, metastatic AAP-naïve, and metastatic post-AAP). The assay was selected because of its increased sensitivity versus an AR exon 8 sequencing approach used by others [13].

Overall, we tested 5 mutations derived from 11 possible amino acid alterations in 5 codons (supplementary Table S1, available at *Annals of Oncology* online) for which the assay was designed, including: F877L ($n=5$), T878A ($n=4$), W742C ($n=1$), V716M ($n=1$) and H875Y ($n=2$). The most common (occurring in more than one subject) were *AR* F877L and *AR* T878A, LBD mutations associated in laboratory models and in the clinic with resistance to enzalutamide and apalutamide (*AR* F877L) [14, 18, 19] and abiraterone (*AR* T878A) [15, 16].

The frequency of *AR* F877L mutations (i.e. copies of mutant AR per genomic equivalent) increased in the mCRPC cohort after exposure to apalutamide, suggesting the possibility of preexisting clones that underwent positive selection with treatment. The 2 patients with the *AR* F877L mutations at baseline had a 12-week PSA decline of >50% after treatment with apalutamide. Notably, both had a relatively low frequency of the mutation at baseline (<0.05%) that increased at the time of progression. Another AAP-naïve mCRPC patient remained on study for 24.9 months and acquired the *AR* F877L mutation at progression (mutation frequency, 0.72%), suggesting a possible mechanism for secondary resistance. *AR* F877L was not detected in any post-AAP mCRPC patients at baseline. One post-AAP patient acquired the *AR* F877L mutation at progression on apalutamide; however, this patient had a low frequency of the mutation (0.04%) and was only on study for 3.4 months with a rising PSA, potentially suggesting a method of resistance other than development of *AR* F877L in the setting of prior AAP exposure.

All patients in our study who harbored the *AR* T878A mutation were in the mCRPC post-AAP cohort, consistent with the results of a recent analysis showing that AR T878A was associated with resistance to abiraterone [13] and consistent with prevalence reported in prior studies [13, 16], whereas *AR* T878A was never detected in patients with nmCRPC or in those in the AAP-naïve mCRPC cohort. One of the patients who lost the *AR* T878A mutation at progression initially had a PSA elevation but subsequently experienced a robust PSA decline and was on treatment for 12 months until treatment discontinuation due to PSA, radiographic and clinical progression. The decrease or loss of the *AR* T878A mutation observed in 2 of the 3 post-AAP patients who received treatment with apalutamide suggests 3 possibilities: apalutamide may have selectively inhibited the clone with this mutation and restored sensitivity to AR-directed treatment; discontinuation of abiraterone may have removed the evolutionary selection pressure that encouraged this AR mutation to emerge during abiraterone treatment; or discontinuation may have removed selective advantage of progesterones with the availability of endogenous steroids.

Blood samples were collected from 93 patients at baseline and from 82 patients at progression using a BEAMing assay designed to detect 11 selected AR-LBD mutations. These mutations were found at a relatively low incidence and frequency. Potential limitations of the analysis include the use of only one assay (limited to one assay per study sample availability) predesigned to detect 11 AR-LBD mutations already known to be associated with resistance to AR signaling-directed therapies. There may be other as of yet not well defined AR-LBD mutations that contribute to resistance. For example, the clinical significance of emergence of *AR* L702H in patients treated with exogenous glucocorticoids was not known when this study was designed [30]. Larger, prospective studies using assays that can detect mutations as well as other alterations in the receptor such as the AR splice variants [12, 31] to more completely address the question of the role of AR-LBD mutations in both *de novo* and acquired resistance would require a different type of blood sample. Given the high sensitivity of the BEAMing assay, it is likely that the *AR* F877L and *AR* T878A mutations are not major contributors to *de novo* or acquired resistance with apalutamide. It is also possible that the presence of *AR* F877L and *AR* T878A mutations in apalutamide-treated patients is an epiphenomenon associated with clonal selection pressures rather than being a driver of apalutamide resistance. Notably, however, preclinical data strongly suggest that these AR mutations confer resistance to AR-targeting agents. Ultimately, an integrated analysis of tumor-specific mRNA and DNA would be required to study the full complement of AR aberrations in men receiving novel hormonal therapies.

Conclusions

Although *AR* F877L has previously been associated with resistance to apalutamide and enzalutamide, patients with CRPC who were treated with apalutamide in our study had a low rate of *de novo* acquisition of the *AR* F877L mutation [3 of 82 patients (4%)] even using the sensitive BEAMing method. Not surprisingly, in patients without prior exposure to second-generation AR antagonists, *AR* F877L was detected at a low frequency at baseline [2 of 93 (2%)], and the presence of these mutations did not preclude PSA declines with apalutamide. The increased frequency of the mutation at the time of progression does suggest that *AR* F877L mutation may contribute to apalutamide resistance, although the frequency of these mutations in patients progressing on apalutamide in this study was low.

Second-line therapy with apalutamide in 2 post-AAP patients resulted in either a decrease or a loss of the preexisting *AR* T878A mutation while on therapy. Given the low frequency of the *AR* F877L and *AR* T878A mutations, they are unlikely to play a dominant role in the mechanism of primary or acquired resistance to apalutamide in CRPC patients.

Acknowledgements

Writing assistance was provided by Lashon Pringle, PhD, and Ira Mills, PhD, of PAREXEL, and was funded by Janssen Global Services, LLC.

Funding

This study was funded by Aragon Pharmaceuticals, Inc. Janssen Research & Development, LLC, is performing work on behalf of Aragon. No grant number is applicable. Dr. Rathkopf and Dr. Scher received support through the NIH/NCI Cancer Center Support Grant P30 CA008748.

Disclosure

DER reports a consultant or advisory role at Janssen Oncology and research funding from Janssen Oncology, Medivation,

Celgene, Takeda, Millennium, Ferring and Novartis; MRS reports a consultant role at Janssen Research & Development; CJR reports a consultant or advisory role at Bayer and Millennium; honoraria from Janssen Oncology and Astellas Pharma; and research funding from BIND Biosciences, Karyopharm Therapeutics and Novartis; WRB reports research grants from AHRQ; NDS reports a consultant or advisory role at Astellas Pharma, Bayer, Janssen Scientific Affairs, Dendreon, Sanofi, Takeda, Tolmar and Ferring; GL and MS have declared no conflicts of interest; CSH reports consulting fees or honoraria from AbbVie, Algeta, Astellas, Bayer, Dendreon, Genentech, Johnson & Johnson, Medivation, Novartis, Pfizer and Veridex; grants or research support from Amgen, Aragon Pharmaceuticals, AstraZeneca, Bayer, Dendreon, Exelixis, Genentech, Johnson & Johnson, Medivation, Millennium, Novartis, OncoGenex, Sanofi-Aventis US, Taxynergy and Teva; and other financial benefit from Cell Therapeutics; JJA reports institutional research funding from Aragon Pharmaceuticals, Janssen Oncology, Astellas Pharma, Millenium, Novartis and Zenith Epigenetics; income for consulting with Astellas Pharma and for educational sessions with Bayer HealthCare Pharmaceuticals; RJH reports stock ownership in Aethlon; honoraria from Best Doctors, Inc.; research funding from US Oncology, Bavarian Nordic, Bristol-Myers Squibb, Merck and Amgen; remuneration for an ABIM Subspecialty Board; and has a patent pending on an immunotherapeutic agent; RFT reports a consultant or advisory role at Medivation/Astellas; stock ownership in Nymox and Sophiris Bio Inc.; honoraria from Nymox; research funding from Nymox, Medivation/Astellas, Janssen Oncology, Sophiris Bio Inc., Bayer, American Medical Systems, Boston Scientific, Advaxis, MDxHealth and Genomic Health; and has served on speakers' bureaus for Medivation/Astellas and Dendreon; ECM reports employment at Aragon Pharmaceuticals (past); ST, DSR, MKY, AT, TK and RB report employment at Janssen Research & Development and stock ownership in Johnson & Johnson; CJdB reports employment at Janssen Biologics and stock ownership in Johnson & Johnson; HIS reports institutional research funding from Exelixis, Innocrin, Medivation, Janssen, Aragon Pharmaceuticals, and Illumina; a consultant or advisory role at Astellas, Sanofi, Millenium, and WCG Oncology (compensated), and at Medivation, Janssen, and Aragon Pharmaceuticals (uncompensated); and receipt of travel, accommodations, and expenses from Astellas, Janssen, Millenium, and Sanofi; ESA reports a consultant or advisory role at Sanofi, Dendreon, Medivation, Janssen Biotech, ESSA and Astellas Pharma; honoraria from Sanofi, Dendreon, Medivation, Janssen Biotech, ESSA and Astellas Pharma; research funding from Janssen Biotech, Johnson & Johnson, Sanofi, Dendreon, Aragon Pharmaceuticals, Exelixis, Millennium, Genentech, Novartis, Astellas Pharma and Tokai Pharmaceuticals; and receipt of travel, accommodations and expenses from Sanofi, Dendreon and Medivation.

References

1. Chi KN, Bjartell A, Dearnaley D et al. Castration-resistant prostate cancer: from new pathophysiology to new treatment targets. Eur Urol 2009; 56: 594–605.
2. Antonarakis ES, Eisenberger MA. Expanding treatment options for metastatic prostate cancer. N Engl J Med 2011; 364: 2055–2058.
3. Chen CD, Welsbie DS, Tran C et al. Molecular determinants of resistance to antiandrogen therapy. Nat Med 2004; 10: 33–39.
4. Clegg NJ, Wongvipat J, Joseph JD et al. ARN-509: a novel antiandrogen for prostate cancer treatment. Cancer Res 2012; 72: 1494–1503.
5. Rathkopf DE, Morris MJ, Fox JJ et al. Phase I study of ARN-509, a novel antiandrogen, in the treatment of castration-resistant prostate cancer. J Clin Oncol 2013; 31: 3525–3530.
6. Rathkopf D, Scher HI. Androgen receptor antagonists in castration-resistant prostate cancer. Cance J 2013; 19: 43–49.
7. Azad AA, Eigl BJ, Murray RN et al. Efficacy of enzalutamide following abiraterone acetate in chemotherapy-naive metastatic castration-resistant prostate cancer patients. Eur Urol 2015; 67: 23–29.
8. Brasso K, Thomsen FB, Schrader AJ et al. Enzalutamide antitumour activity against metastatic castration-resistant prostate cancer previously treated with docetaxel and abiraterone: a multicentre analysis. Eur Urol 2015; 68: 317–324.
9. Loriot Y, Bianchini D, Ileana E et al. Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100). Ann Oncol 2013; 24: 1807–1812.
10. Noonan KL, North S, Bitting RL et al. Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide. Ann Oncol 2013; 24: 1802–1807.
11. Antonarakis ES, Lu C, Wang H et al. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. N Engl J Med 2014; 371: 1028–1038.
12. Scher HI, Lu D, Schreiber NA et al. Association of AR-V7 on circulating tumor cells as a treatment-specific biomarker with outcomes and survival in castration-resistant prostate cancer. JAMA Oncol 2016; 2: 1441–1449.
13. Azad AA, Volik SV, Wyatt AW et al. Androgen receptor gene aberrations in circulating cell-free DNA: biomarkers of therapeutic resistance in castration-resistant prostate cancer. Clin Cancer Res 2015; 21: 2315–2324.
14. Balbas MD, Evans MJ, Hosfield DJ et al. Overcoming mutation-based resistance to antiandrogens with rational drug design. Elife 2013; 2: e00499.
15. Cai C, Chen S, Ng P et al. Intratumoral de novo steroid synthesis activates androgen receptor in castration-resistant prostate cancer and is upregulated by treatment with CYP17A1 inhibitors. Cancer Res 2011; 71: 6503–6513.
16. Chen EJ, Sowalsky AG, Gao S et al. Abiraterone treatment in castration-resistant prostate cancer selects for progesterone responsive mutant androgen receptors. Clin Cancer Res 2015; 21: 1273–1280.
17. Hara T, Miyazaki J, Araki H et al. Novel mutations of androgen receptor: a possible mechanism of bicalutamide withdrawal syndrome. Cancer Res 2003; 63: 149–153.
18. Joseph JD, Lu N, Qian J et al. A clinically relevant androgen receptor mutation confers resistance to second-generation antiandrogens enzalutamide and ARN-509. Cancer Discov 2013; 3: 1020–1029.
19. Korpal M, Korn JM, Gao X et al. An F876L mutation in androgen receptor confers genetic and phenotypic resistance to MDV3100 (enzalutamide). Cancer Discov 2013; 3: 1030–1043.
20. Taplin ME, Bubley GJ, Ko YJ et al. Selection for androgen receptor mutations in prostate cancers treated with androgen antagonist. Cancer Res 1999; 59: 2511–2515.
21. Gottlieb B, Beitel LK, Nadarajah A et al. The androgen receptor gene mutations database (ARDB): 2012 update. Hum Mutat 2012; 33: 887–894.
22. Lallous N, Volik SV, Awrey S et al. Functional analysis of androgen receptor mutations that confer anti-androgen resistance identified in circulating cell-free DNA from prostate cancer patients. Genome Biol 2016; 17: 10.
23. Prekovic S, van Royen ME, Voet AR et al. The effect of F877L and T878A mutations on androgen receptor response to enzalutamide. Mol Cancer Ther 2016; 15: 1702–1712.

24. Romanel A, Gasi TD, Conteduca V et al. Plasma AR and abiraterone-resistant prostate cancer. Sci Transl Med 2015; 7: 312re10.
25. Smith MR, Antonarakis ES, Ryan CJ et al. Phase 2 study of the safety and antitumor activity of apalutamide (ARN-509), a potent androgen receptor antagonist, in the high-risk nonmetastatic castration-resistant prostate cancer cohort. Eur Urol 2016; 70: 963–970.
26. Rathkopf DE, Antonarakis ES, Shore ND et al. Safety and antitumor activity of apalutamide (ARN-509) in metastatic castration-resistant prostate cancer with and without prior abiraterone acetate and prednisone. Clin Cancer Res 2017 February 17 [epub ahead of print], doi:10.1158/1078-0432.CCR-16-2509.
27. Scher HI, Halabi S, Tannock I et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 2008; 26: 1148–1159.
28. Richardson AL, Iglehart JD. BEAMing up personalized medicine: mutation detection in blood. Clin Cancer Res 2012; 18: 3209–3211.
29. Wyatt AW, Azad AA, Volik SV et al. Genomic alterations in cell-free DNA and enzalutamide resistance in castration-resistant prostate cancer. JAMA Oncol 2016; 2: 1598–1606.
30. Carreira S, Romanel A, Goodall J et al. Tumor clone dynamics in lethal prostate cancer. Sci Transl Med 2014; 6: 254ra125.
31. Antonarakis ES, Lu C, Luber B et al. Androgen receptor splice variant 7 and efficacy of taxane chemotherapy in patients with metastatic castration-resistant prostate cancer. JAMA Oncol 2015; 1: 582–591.

Original Study

Effect of Visceral Disease Site on Outcomes in Patients With Metastatic Castration-resistant Prostate Cancer Treated With Enzalutamide in the PREVAIL Trial

Joshi J. Alumkal,[1] Simon Chowdhury,[2] Yohann Loriot,[3] Cora N. Sternberg,[4] Johann S. de Bono,[5] Bertrand Tombal,[6] Joan Carles,[7] Thomas W. Flaig,[8] Tanya B. Dorff,[9] De Phung,[10] David Forer,[11] Sarah B. Noonberg,[12] Hank Mansbach,[12] Tomasz M. Beer,[1] Celestia S. Higano[13]

Abstract

We assessed outcomes from men with metastatic castration-resistant prostate cancer that had spread to the liver and/or lungs in the PREVAIL clinical trial of enzalutamide in patients who had not received docetaxel chemotherapy. Compared with placebo, enzalutamide lengthened the time it took for the cancers to grow (according to changes in scans), prostate-specific antigen to rise, or patients to require chemotherapy.

Background: The Multinational Phase 3, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Oral MDV3100 in Chemotherapy-Naive Patients With Progressive Metastatic Prostate Cancer Who Have Failed Androgen Deprivation Therapy (PREVAIL) trial was unique as it included patients with visceral disease. This analysis was designed to describe outcomes for the subgroup of men from PREVAIL with specific sites of visceral disease to help clinicians understand how these patients responded to enzalutamide prior to chemotherapy. **Patients and Methods:** Prespecified analyses examined the coprimary endpoints of radiographic progression-free survival (rPFS) and overall survival (OS) only. All other efficacy analyses were post hoc. The visceral subgroup was divided into liver or lung subsets. Patients with both liver and lung metastases were included in the liver subset. **Results:** Of the 1717 patients in PREVAIL, 204 (12%) had visceral metastases at screening (liver only or liver/lung metastases, n = 74; lung only metastases, n = 130). In patients with liver metastases, enzalutamide was associated with an improvement in rPFS (hazard ratio [HR], 0.44; 95% confidence interval [CI], 0.22-0.90) but not OS (HR, 1.04; 95% CI, 0.57-1.87). In patients with lung metastases only, the HR for rPFS (0.14; 95% CI, 0.06-0.36) and the HR for OS (0.59; 95% CI, 0.33-1.06) favored enzalutamide over placebo. Patients with liver metastases had worse outcomes than those with lung metastases, regardless of treatment. Enzalutamide was well tolerated in patients with visceral disease. **Conclusions:** Enzalutamide is an active first-line treatment option for men with asymptomatic or mildly symptomatic chemotherapy-naive metastatic castration-resistant prostate cancer and visceral disease. Patients with lung-only disease fared better than patients with liver disease, regardless of treatment.

Clinical Genitourinary Cancer, Vol. 15, No. 5, 610-17
Keywords: Androgen receptor inhibitor, Chemotherapy-naive, Metastases, Phase III, Survival analysis

Medivation was acquired by Pfizer Inc, in September 2016.

[1]OHSU Knight Cancer Institute, Oregon Health & Science University, Portland, OR
[2]Department of Medical Oncology, Guy's Hospital, London, UK
[3]Department of Cancer Medicine, Gustave Roussy, University of Paris-Sud, Villejuif, France
[4]Department of Medical Oncology, San Camillo and Forlanini Hospitals, Rome, Italy
[5]Division of Clinical Studies, Royal Marsden Hospital and Institute of Cancer Research, London, UK
[6]Department of Urology, Cliniques universitaires Saint-Luc, Brussels, Belgium
[7]Department of Medical Oncology, Vall d'Hebron University Hospital, and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain
[8]Department of Medicine, University of Colorado School of Medicine, Aurora, CO
[9]Department of Medical Oncology, USC Norris Cancer Hospital, Keck Medical Center of USC, Los Angeles, CA
[10]Department of Biostatistics, Astellas Pharma Europe, BV, Leiden, Netherlands
[11]Department of Biostatistics, Medivation, Inc, San Francisco, CA
[12]Department of Clinical Development, Medivation, Inc, San Francisco, CA
[13]Division of Medical Oncology, University of Washington, Fred Hutchinson Cancer Research Center, Seattle, WA

Submitted: Dec 14, 2016; Revised: Feb 6, 2017; Accepted: Feb 19, 2017; Epub: Mar 3, 2017

Address for correspondence: Joshi J. Alumkal, MD, Oregon Health & Science University, Knight Cancer Institute, Mail Code: CH14R, 3303 SW Bond Ave, Portland, OR 97239
E-mail contact: alumkalj@ohsu.edu

1558-7673/$ - see frontmatter
http://dx.doi.org/10.1016/j.clgc.2017.02.007

Introduction

Nearly all patients with recurrent prostate cancer or de novo metastatic disease treated with androgen deprivation therapy eventually develop castration-resistant prostate cancer (CRPC), the lethal form of this disease.[1,2] Survival of patients with metastatic CRPC (mCRPC) is usually < 3 years, with > 26,000 deaths predicted in the United States alone in 2016.[3-7] Patients with mCRPC with visceral disease, most commonly in the liver and/or lung, are thought to have a particularly poor prognosis, and the presence of liver metastases is associated with the shortest survival.[3,4,8,9]

During the drug development process, patients with mCRPC have been previously categorized by docetaxel chemotherapy exposure, the first drug to improve overall survival (OS) for men with mCRPC in phase III trials.[10,11] Studies of systemic agents in the post-docetaxel setting have generally included men with visceral disease.[12-14] However, phase III trials in the pre-docetaxel setting have excluded these patients because of the widespread belief that docetaxel, rather than an investigational agent, is the preferred treatment option for patients with visceral disease given their poor prognosis.[15,16] The Multinational Phase 3, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Oral MDV3100 in Chemotherapy-Naive Patients With Progressive Metastatic Prostate Cancer Who Have Failed Androgen Deprivation Therapy (PREVAIL) trial (ClinicalTrials.gov number: NCT01212991) challenged this view by enrolling patients with visceral disease, provided they were otherwise eligible based on performance criteria (ie, an Eastern Cooperative Oncology Group performance status [ECOG PS] of 0 or 1 and a score of 0 to 3 on Brief Pain Inventory Short Form question 3).[5] PREVAIL was designed with the expectation that minimally symptomatic men with good ECOG PS would be followed carefully with imaging studies and could receive an investigational therapy or placebo and still receive chemotherapy after discontinuing the study medication.

In PREVAIL, enzalutamide significantly improved OS and radiographic progression-free survival (rPFS) relative to placebo in the overall population of men with chemotherapy-naive mCRPC.[5] A prespecified subgroup analysis of PREVAIL data revealed that treatment with enzalutamide reduced the risk of the composite endpoint of radiographic progression or death by 72% (hazard ratio [HR], 0.28; 95% confidence interval [CI], 0.16-0.49) but not risk of death (HR, 0.82; 95% CI, 0.55-1.23) in patients with visceral disease, defined as a combined population with baseline disease in the liver and/or lung, with or without metastases to the bone or lymph nodes.[17] Outcomes for patients with lymph node-only disease were also analyzed in this subgroup analysis.[17] The current analysis of PREVAIL determines how outcomes with enzalutamide versus placebo treatment were affected by the specific site of visceral disease (ie, liver metastases vs. lung-only metastases). Moreover, this analysis provides information on the natural history of chemotherapy-naive patients with mCRPC and liver or lung-only visceral disease treated in the placebo arm.

Patients and Methods

Study Design and Participants

The PREVAIL study design, eligibility criteria, and conduct have been fully described elsewhere.[5] Patients were randomized to either oral enzalutamide 160 mg/day or placebo until the occurrence of unacceptable adverse events, or confirmed radiographic progression and the initiation of chemotherapy or an investigational agent. The study was approved by the independent review board at each participating site, and was conducted in compliance with the ethical principles originating in or derived from the provisions of the Declaration of Helsinki and the Good Clinical Practice Guidelines of the International Conference on Harmonisation. All patients provided written informed consent before participating in the trial.

Presence of visceral disease (liver and/or lung) was determined radiographically (computed tomography scan or magnetic resonance imaging) by the treating physician and did not require confirmation by biopsy. For all efficacy analyses, the visceral subgroup was divided into liver and lung subsets. Patients with both liver and lung metastases were included in the liver subset because of the previously described inferior survival outcomes of patients with liver versus lung-only involvement.[3,4,8,9]

The coprimary endpoints of rPFS and OS were prospectively evaluated in the liver and lung subsets along with the exploratory analysis of the following endpoints (all were secondary endpoints in PREVAIL except where indicated): time to initiation of chemotherapy, time to prostate-specific antigen (PSA) progression, time to decline on the Functional Assessment of Cancer Therapy—Prostate questionnaire (FACT-P; exploratory endpoint), confirmed PSA response (≥ 50% PSA decline from baseline), and best overall tissue response determined by investigator assessment using Response Evaluation Criteria In Solid Tumors version 1.1. The coprimary endpoint rPFS was defined as time from randomization to first objective evidence of radiographic disease progression assessed by a blinded independent central review facility or death from any cause within 168 days after treatment discontinuation, whichever occurred first.

Statistical Analysis

The Kaplan-Meier product limit method was used to estimate distributions of the time to events. HRs and their 95% CIs were estimated using an unstratified Cox regression model. A 2-sided, unstratified log-rank test was used to compare rPFS and OS between enzalutamide and placebo. The primary analysis was by intention-to-treat, defined as those patients with measurable disease at screening who were then randomized to one of the treatment arms.

Cochran-Mantel-Haenszel score tests were used to compare the proportion of enzalutamide- and placebo-treated patients with a confirmed ≥ 50% reduction in PSA from baseline to PSA nadir and objective response, with corresponding 2-sided 95% CIs calculated using the Clopper-Pearson method.

Incidence data were used to assess the safety and tolerability of enzalutamide and placebo. To adjust for differences in duration of study treatment between the enzalutamide and placebo groups, adverse events (AEs) were also evaluated using event-rate calculations (events per 100 patient-years).

The results presented herein are based on a cutoff date of September 16, 2013, except for rPFS, which was based on a data cutoff date of May 6, 2012.

Results

Patients and Treatment

In PREVAIL, 1717 patients were randomized to treatment: 872 to enzalutamide and 845 to placebo (See Supplemental Figure 1 in the online version). Overall, 204 patients had visceral disease at baseline: 98 (11%) in the enzalutamide group and 106 (13%) in the placebo group (Table 1). Among patients with visceral disease, liver metastases (in 36% of patients) were less frequent than lung metastases (in 64% of patients). Six (0.7%) patients in the enzalutamide group and 3 (0.4%) in the placebo group had both liver and lung metastases and were included in the liver subset.

In the visceral subgroup, patient demographics and disease characteristics were generally similar between treatment arms (Table 1). Liver and lung subsets were well-balanced between each other and the full population with respect to patient age, ECOG PS, median Gleason score, baseline levels of hemoglobin and albumin, baseline pain, and presence of bone disease. A greater proportion of patients in the liver subset than those in the lung subset and full population had more than 20 bone metastases (Table 1). Patients with liver metastases also had higher baseline levels of lactate dehydrogenase, alkaline phosphatase, and PSA than those with lung metastases and those in the full population.

In both the liver and lung subsets, the duration of treatment was longer with enzalutamide than placebo (Table 2). However, the duration of enzalutamide and placebo treatment was shorter in the liver subset than the lung subset and full population.

Efficacy

Coprimary Endpoints. Treatment with enzalutamide versus placebo reduced the risk of radiographic progression or death by 56% in patients with liver metastases and by 86% in patients with lung metastases (Figure 1). The HR in the lung subset (0.14) was similar to that in the full population (0.19).[5] The HR in the smaller subset of patients with liver metastases favored enzalutamide (0.44), although the magnitude of benefit was less than in the lung subset or the full population. In both treatment groups, median rPFS was shorter in patients with liver metastases than in those with lung metastases.

Treatment with enzalutamide versus placebo was not associated with a reduced risk of death in the subsets of patients with liver and/or lung metastases (Figure 2). In the liver subset, median OS was 18.9 months (interquartile range [IQR], 10.7-26.2 months) with enzalutamide and 14.8 months (IQR, 8.9 months to not yet reached [NYR]) with placebo, both considerably shorter than that observed in either the lung subset or full population.[5] Median OS with enzalutamide in the lung subset (32.4 months; IQR, 20.9 months to NYR) was identical to that of patients in the full population receiving enzalutamide (32.4 months; IQR, 22.0 months to NYR[5]), and indicated some improvement in median OS over placebo (26.0 months; IQR, 14.8 months to NYR) in this subset of patients.

A post hoc test of the interaction between treatment and visceral status was not significant for rPFS ($P = .2231$) or OS ($P = .4755$).

Secondary and Exploratory Endpoints. In both the liver and lung subsets, treatment with enzalutamide versus placebo was associated with improvements in all secondary endpoints (Figure 3), including delaying time to initiation of chemotherapy (by approximately 15 and 18 months, respectively), which was similar to that in the full population (approximate delay of 17 months). In both visceral subsets, treatment with enzalutamide was associated with delaying time to PSA progression. Confirmed PSA response rates ($\geq$ 50% decline) with enzalutamide were 51% in the liver subset (0% with placebo) and 94% in the lung subset (3% with placebo). In the full population, PSA response rates were 78% with enzalutamide and 3% with placebo.[5] The small subset of patients with liver metastases fared worse than those with lung metastases, who had benefits on secondary endpoints consistent with the full population. Enzalutamide did not delay time to FACT-P decline in the visceral subsets versus placebo, which was not the case in the full population.[5]

In patients with measurable disease at baseline, best overall soft-tissue response rate with enzalutamide was 29% (10 of 34 patients) in the liver subset and 73% (27 of 37 patients) in the lung subset, and 3% (1 of 30 patients) and 0% (0 of 50 patients), respectively, with placebo. Six patients with visceral disease—2 (6%) with liver metastases and 4 (11%) with lung metastases—achieved a complete response with enzalutamide. Radiographic images showing the disappearance of liver and lung lesions in 2 patients with a complete response to enzalutamide are shown in Supplemental Figure 2 (in the online version).

Safety

The incidence of any AE, grade 3 or 4 AEs, and serious AEs in the visceral subgroup were similar to those in the full study population (See Supplemental Table 1 in the online version). The incidence rate of the most common AEs of fatigue, back pain, constipation, and arthralgia were each lower with enzalutamide than placebo; among specific AEs, rates of hypertension (11 vs. 8 per 100 patient-years) and cardiac AEs (19 vs. 15 per 100 patient-years) were higher with enzalutamide, which was consistent with findings in the full population (See Supplemental Table 1 in the online version).

Subsequent Therapies

More patients in the placebo arms of the nonvisceral and visceral subgroups received chemotherapy (either docetaxel or cabazitaxel) as the first subsequent therapy after progression (Table 3).

Discussion

The PREVAIL trial included patients with visceral disease who were asymptomatic or minimally symptomatic, had ECOG PS of 0 or 1, and were chemotherapy-naive. Men in the placebo arm also represent the first prospectively followed group with CRPC and visceral disease stratified by specific anatomical site to be reported.

It is important for clinicians to understand how the subgroup of men with baseline visceral disease located at common sites of metastasis did with second-line hormone therapy prior to chemotherapy. A prior analysis showed that enzalutamide versus placebo reduced the risk of rPFS but not OS in the 204 PREVAIL patients with baseline visceral disease at any site.[17] Our analysis extends these findings by assessing enzalutamide efficacy specifically by the site of metastasis. Although patients with liver metastases had delayed radiographic progression and improvements on all progression and response endpoints, including complete responses in 2 (6%) patients, enzalutamide treatment did not improve OS in that subset.

Table 1 Baseline Patient and Disease Characteristics in the PREVAIL Visceral Subgroups and Full Population

Parameter	Liver Metastases		Lung Metastases		Full Study Population	
	Enzalutamide (n = 40)	Placebo (n = 34)	Enzalutamide (n = 58)	Placebo (n = 72)	Enzalutamide (n = 872)	Placebo (n = 845)
Median age, y (IQR)	74.0 (70.0-81.5)	70.0 (65.0-75.0)	73.0 (66.0-78.0)	71.0 (65.0-76.5)	72.0 (66.0-78.0)	71.0 (65.0-77.0)
ECOG PS, n (%)						
0	22 (55)	23 (68)	37 (64)	44 (61)	584 (67)	585 (69)
1	18 (45)	11 (32)	21 (36)	28 (39)	288 (33)	260 (31)
Baseline pain score on BPI-SF Q3, n (%)[a]						
0-1	22 (56)	24 (73)	38 (66)	41 (57)	569 (66)	567 (68)
≥2	17 (44)	9 (27)	20 (35)	31 (43)	290 (34)	273 (33)
Median lactate dehydrogenase, U/L (IQR)	204.5 (176.5-307.0)	218.5 (190.0-324.0)	180.5 (154.0-212.0)	190.0 (170.0-221.0)	185.0 (164.0-218.0)	185.0 (164.0-217.0)
Median alkaline phosphatase, U/L (IQR)	112.0 (77.5-168.0)	126.5 (77.0-298.0)	91.5 (71.0-119.0)	89.0 (70.0-131.0)	94.0 (70.0-138.0)	86.0 (68.0-126.0)
Median PSA, ng/mL (IQR)	83.9 (35.5-259.1)	104.3 (30.5-289.7)	70.2 (16.5-152.2)	51.2 (13.7-156.3)	54.1 (17.7-130.9)	44.2 (17.0-132.2)
Median hemoglobin, g/L (IQR)	128.5 (116.5-137.0)	127.0 (120.0-134.0)	130.0 (121.0-137.0)	130.0 (124.0-139.0)	130.0 (123.0-138.0)	131.0 (123.0-138.0)
Median albumin, g/L (IQR)	37.5 (36.0-41.5)	37.0 (35.0-39.0)	39.0 (36.0-41.0)	38.0 (36.0-40.0)	38.0 (36.0-40.0)	39.0 (36.0-40.0)
Median Gleason score (IQR)	8.0 (7.0-9.0)	7.0 (7.0-9.0)	7.0 (7.0-8.0)	7.0 (7.0-9.0)	8.0 (7.0-9.0)	8.0 (7.0-9.0)
Gleason score ≥8 at initial diagnosis, n (%)[a]	22 (56)	15 (47)	21 (38)	34 (49)	424 (51)	423 (52)
Bone disease, n (%)	34 (85)	27 (79)	46 (79)	57 (79)	741 (85)	690 (82)
>20 bone metastases, n (%)	10 (25)	13 (38)	7 (12)	14 (19)	145 (17)	150 (18)
Measurable soft-tissue disease, n (%)	34 (85)	30 (88)	37 (64)	50 (69)	396 (45)	381 (45)
Baseline use of corticosteroids, n (%)	3 (7.5)	2 (5.9)	3 (5.2)	2 (2.8)	35 (4.0)	36 (4.3)
Prior antiandrogen use, n (%)	36 (90)	31 (91)	46 (79)	64 (89)	760 (87)	730 (86)
Prior radical prostatectomy, n (%)	12 (30)	8 (24)	15 (26)	14 (19)	226 (26)	225 (27)

Abbreviations: BPI-SF Q3 = Brief Pain Inventory Short Form question 3; ECOG PS = Eastern Cooperative Oncology Group performance status; IQR = interquartile range; PSA = prostate-specific antigen.
[a]Some patients had missing baseline values. Percentages were calculated based on all patients with baseline values.

Table 2 Duration of Study Drug Treatment in the PREVAIL Visceral Subgroups and Full Population

Parameter	Liver Metastases		Lung Metastases		Full Study Population[a]	
	Enzalutamide (n = 40)	Placebo (n = 34)	Enzalutamide (n = 58)	Placebo (n = 72)	Enzalutamide (n = 871)	Placebo (n = 844)
Duration of treatment, mo						
Median (IQR)	9.6 (3.6-17.6)	3.4 (2.1-4.4)	15.5 (10.6-20.4)	3.9 (2.1-6.9)	16.6 (10.1-21.1)	4.6 (2.8-9.7)
Mean (SD)	10.5 (8.15)	4.8 (4.67)	15.6 (8.21)	5.3 (4.32)	15.8 (7.64)	7.0 (6.05)
Patients with ≥12 months of treatment duration, %	32	8.8	55	4.2	68	18
Treatment ongoing at data cutoff date, %	20	0	36	2.8	42	7.2
Median OS follow-up, mo (IQR)	22.9 (17.4-27.2)	25.1 (20.5-27.8)	22.8 (18.2-29.2)	23.6 (20.9-27.5)	22.2 (18.5-26.7)	22.4 (18.5-26.4)

Abbreviations: IQR = interquartile range; OS = overall survival; SD = standard deviation.
[a]One patient in each treatment group was enrolled but never treated.

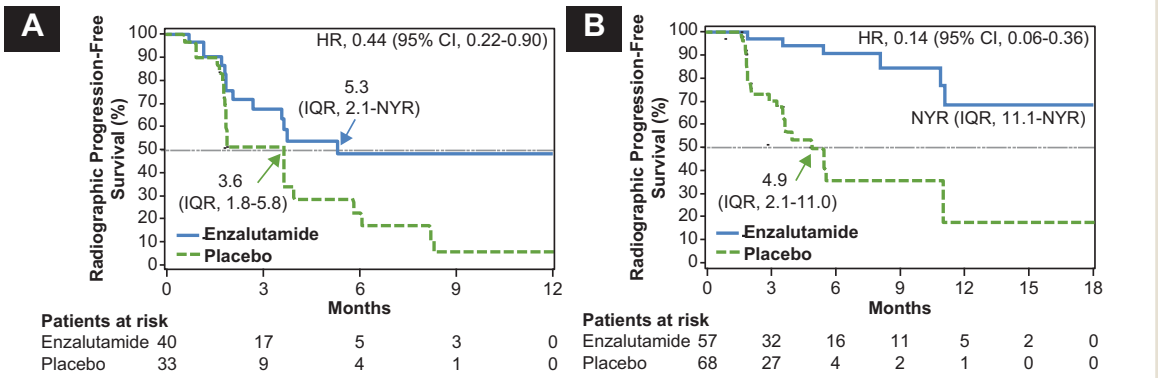
The lack of an effect on survival may have been because of the small number of patients with liver metastases in PREVAIL.

We focused on subsets of patients with liver and lung metastases because these were the most common sites of visceral disease, and we determined that these sites affected rPFS and OS, as well as secondary and exploratory endpoint measures. Patients with liver metastases had a distinctly worse outcome than those with lung metastases. Moreover, patients with lung-only visceral metastases had outcomes similar to patients without any visceral metastases and the overall PREVAIL study population.[5] These findings confirm the poorer prognosis associated with liver metastases regardless of enzalutamide or placebo treatment, which is consistent with prior reports for other agents.[3,4,8,9] We observed that a significant proportion of patients in the visceral and nonvisceral placebo arms were able to receive treatment with chemotherapy after progression on study, supporting the initial reasoning that placebo use in this population would not prevent subsequent treatment with chemotherapy.

Our results suggest a need to better understand the underlying biology of metastatic tumors with a predilection to the liver that leads to inferior treatment responses and outcomes in patients with CRPC regardless of the treatment prescribed. For those with lung-only metastases, improvements in rPFS, OS, and secondary endpoints were similar to those observed in the overall PREVAIL population. These findings suggest that the category of "visceral disease" should be divided into lung-only and liver and not analyzed separately, at least in this population of chemotherapy-naive men with mCRPC.

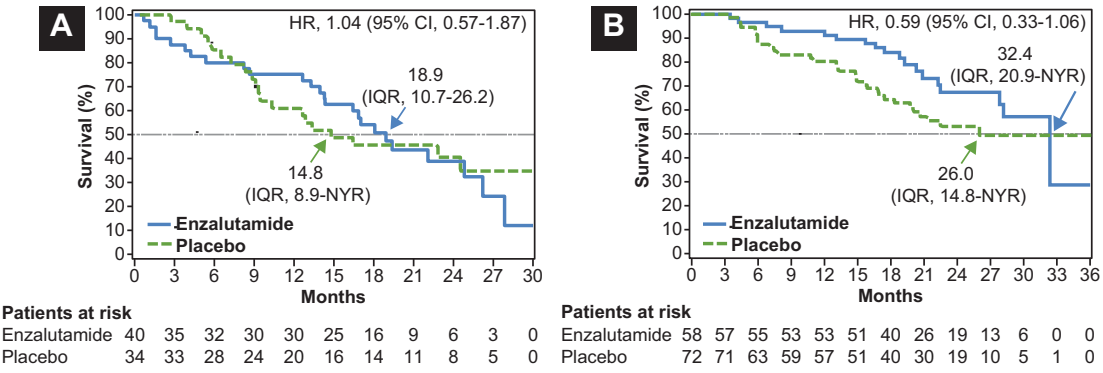
There is limited information on efficacy outcomes for chemotherapy-naive patients with mCRPC with visceral disease treated with systemic therapies other than chemotherapy. In the TAX 327 study, docetaxel plus prednisone improved survival compared with mitoxantrone plus prednisone in men with mCRPC.[10] An updated survival analysis that combined all patients who received chemotherapy in TAX 327 showed that patients with visceral disease (liver or lung sites not specified), who comprised 23% of the overall study population, died earlier than those without visceral disease.[18] A subsequent retrospective analysis that evaluated outcomes by site of visceral disease showed PSA response rates of 22% and 31% in patients with liver or lung metastases and radiographic response rates of 6% and 7%, respectively.[4] In comparison, patients with liver or lung metastases treated with enzalutamide in

Figure 1 Kaplan-Meier Estimates of Radiographic Progression-free Survival in Patients With Metastatic Castration-resistant Prostate Cancer Who Participated in the Phase III PREVAIL Trial and Had Metastatic Liver (A) or Lung (B) Disease



Abbreviations: CI = confidence interval; HR = hazard radio; IQR = interquartile range; NYR = not yet reached.

Figure 2 Kaplan-Meier Estimates of Overall Survival in Patients With Metastatic Castration-resistant Prostate Cancer Who Participated in the Phase III PREVAIL Trial and Had Metastatic Liver (A) or Lung (B) Disease

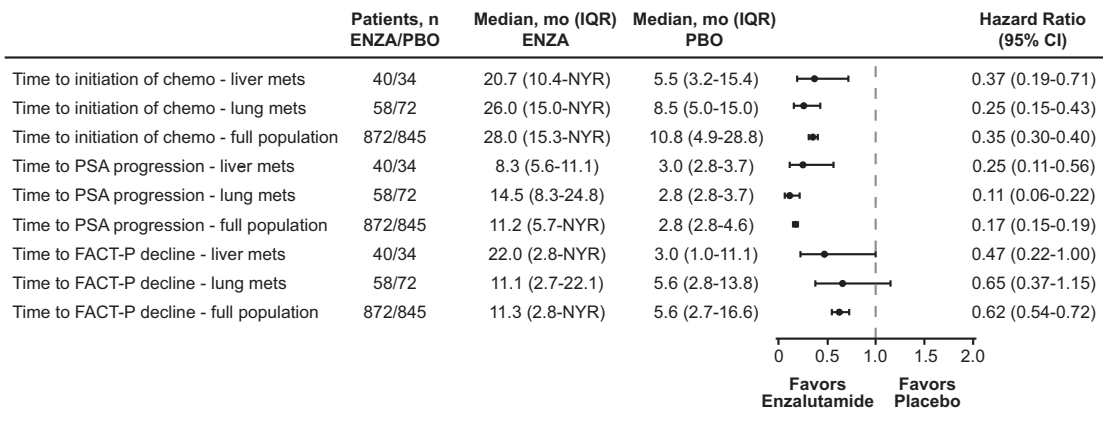


Abbreviations: CI = confidence interval; HR = hazard ratio; IQR = interquartile range; NYR = not yet reached.

our analysis had PSA response rates of 51% and 94% and radiographic response rates of 29% and 73%, respectively. Complete responses were observed in individual patients with liver (6%) or lung (11%) metastases. Although the TAX 327 and PREVAIL trial populations and designs are not directly comparable and they were conducted more than a decade apart, our analysis suggests that enzalutamide has substantial clinical activity in chemotherapy-naive patients with mCRPC with visceral disease, regardless of the site of visceral involvement.

Several strengths and limitations of our analysis should be noted. PREVAIL was the first phase III study of chemotherapy-naive men with mCRPC with minimal or no symptoms to include patients with visceral disease. Liver and lung subsets were prospectively defined in terms of number and sites of involvement as recommended by the Prostate Cancer Clinical Trials Working Group 2.[19] However, because presence of visceral disease (liver and/or lung) was determined radiographically by the treating physician and did not require confirmation by biopsy, it is possible that some of the lesions were not accurately attributed. Although enzalutamide was effective in chemotherapy-naive patients with mCRPC with visceral disease, it is likely that other agents that target androgen receptor signaling, such as abiraterone acetate, may also be efficacious. This assertion remains unresolved as the Phase 3, Randomized, Double-blind, Placebo-Controlled Study of Abiraterone Acetate (CB7630) Plus Prednisone in Asymptomatic or Mildly Symptomatic Patients With Metastatic Castration-Resistant Prostate Cancer (COU-302) trial excluded men with visceral disease.[15] Finally, the total number of patients with liver or lung metastases was small compared with the nonvisceral

Figure 3 Secondary Efficacy Outcomes in the PREVAIL Visceral Subgroups and Full Population



Abbreviations: Chemo = chemotherapy; CI = confidence interval; ENZA = enzalutamide; FACT-P = Functional Assessment of Cancer Therapy—Prostate questionnaire; IQR = interquartile range; mets = metastases; NYR = not yet reached; PBO = placebo; PSA = prostate-specific antigen.

Table 3 All Subsequent Postbaseline Antineoplastic Therapy Use for Metastatic Castration-resistant Prostate Cancer in PREVAIL

Parameter	Nonvisceral Subgroup (n = 1513)		Visceral Subgroup (n = 204)	
	Enzalutamide (n = 774)	Placebo (n = 739)	Enzalutamide (n = 98)	Placebo (n = 106)
Patients with ≥1 postbaseline therapy listed below	307 (40)	516 (70)	44 (45)	78 (74)
Antineoplastic therapy				
Abiraterone acetate	157 (20)	340 (46)	22 (22)	45 (43)
Cabazitaxel	40 (5.2)	93 (13)	11 (11)	17 (16)
Docetaxel	255 (33)	412 (56)	31 (32)	67 (63)
Enzalutamide	5 (0.6)	29 (3.9)	4 (4.1)	8 (7.5)
Sipuleucel-T	11 (1.4)	7 (0.9)	1 (1.0)	3 (2.8)
Patients taking ≥1 investigational drug	38 (4.9)	69 (9.3)	4 (4.1)	12 (11)

All data are shown as n (%).

subgroup, and PREVAIL was not designed or powered to detect treatment differences within these subsets. Our interpretations of results must therefore be considered exploratory.

Conclusions

Our analysis has relevance for clinical practice by addressing a knowledge gap in the literature regarding the outcomes of men with asymptomatic or minimally symptomatic mCRPC and visceral disease involving the liver and/or lung who were treated with enzalutamide or placebo. Enzalutamide is a reasonable therapeutic option in such patients and appears to be well-tolerated, with a safety profile similar to that observed in the full PREVAIL population. Because of the poorer outcomes in patients with liver metastases than in those with lung metastases observed in this and other studies,[3,4,8,9] it is critical to identify tumor and microenvironment influences that may be responsible. Elucidating the biological differences between metastatic sites of CRPC may enable the development new drug combinations that further improve upon the efficacy of enzalutamide.

Clinical Practice Points

- Enzalutamide significantly decreases the risk of radiographic progression and death, delays the initiation of chemotherapy, and improves health-related quality of life in chemotherapy-naive men with asymptomatic or minimally symptomatic metastatic prostate cancer progressing on androgen-deprivation therapy.
- The PREVAIL trial of the oral androgen-receptor inhibitor enzalutamide versus placebo was unique in that it did not exclude patients with visceral disease. Our analysis revealed that enzalutamide improved rPFS in patients with liver and/or lung disease.
- Enzalutamide may be considered to be an active first-line treatment option in patients with mCRPC, including those with visceral involvement, delaying the need for chemotherapy.

Acknowledgments

This study was funded by Medivation, Inc, and Astellas Pharma, Inc; Medivation was acquired by Pfizer Inc, in September 2016. Authors employed by both study sponsors were involved in the investigation, data validation and analysis, and the writing and approval of the article. Medical writing and editorial support funded by the study sponsors was provided by Malcolm J.M. Darkes, PhD, Timothy Lohret, PhD, and Shannon Davis from Ashfield Healthcare Communications.

Disclosure

J.J.A. has served as an advisor for Gilead Sciences, and has received institutional research funding from Aragon Pharmaceuticals, Astellas, AstraZeneca, Bristol-Myers Squibb, ImClone Systems, Millennium, and Novartis. T.M.B. has stock and other ownership interests in Salarius Pharmaceuticals, has been an advisor for Astellas Pharma, Bayer, Dendreon, Janssen Japan, Novartis, and Sotio, and has received institutional research funding from Astellas, Bristol-Myers Squibb, Dendreon, Janssen Research & Development, Medivation, OncoGenex, and Sotio. J.C. has served as an advisor for Amgen, Astellas, Bayer, BMS, Johnson & Johnson, and Pfizer, and has served on a speakers' bureau for Bayer. S.C. has received honoraria from Astellas, Bayer, Janssen, and Sanofi, has served as advisor for Astellas, Bayer, Essai, Janssen, and Sanofi, has served on speakers' bureaus for Astellas, Bayer, GlaxoSmithKline, Janssen, and Pfizer, and has received research funding from Janssen and Sanofi and travel expenses from Astellas, Bayer, GlaxoSmithKline, and Janssen. J.S.d.B. has received honoraria from and served as an advisor and on a speakers' bureau for Astellas. T.B.D. has received honoraria from and served on speakers' bureaus for Astellas, Pfizer, and Sanofi, has served as an advisor for Dendreon, Genentech, and Medivation, and has received institutional research funding from Bristol-Myers Squibb. T.W.F. has served in a leadership role for and has stock or other ownership interest in Aurora Oncology, has received honoraria from BN ImmunoTherapeutics and GTx, has served as an advisor for GTx, has received research funding from Aragon Pharmaceuticals, Bavarian Nordic, Bristol-Myers Squibb, Cougar Biotechnology, Dendreon, Exelixis, GTx, Janssen Oncology, Medivation, Novartis, Pfizer, Roche/Genentech, Sanofi, Sotio, and Tokai Pharmaceuticals, is the inventor of 2 patents filed by University of Colorado (related to bladder cancer treatment of early-stage disease), and has received travel expenses from Bavarian Nordic and GTx. D.F. is an employee of and has stock options in Medivation. C.S.H. has served as an advisor for AbbVie, Bayer,

BHR Pharma, Dendreon, Emergent BioSolutions, Ferring, Genentech, Medivation, Orion Corporation, Pfizer, and Sanofi, has received institutional research funding from Algeta/Bayer, Aragon Pharmaceuticals, AstraZeneca, Dendreon, Emergent BioSolutions, Exelixis, Genentech, Medivation, Millennium, Oncogenex, Sanofi, and Teva, and has received travel expenses from AbbVie, Amgen, Astellas Pharma, Bayer, Dendreon, Emergent BioSolutions, Ferring, Genentech, Johnson & Johnson, Medivation, Ockham, Orion Pharma, Pfizer, Sanofi, and Teva. Y.L. has served as an advisor for Astellas, Bristol-Myers Squibb, Ipsen, Janssen, Roche, and Sanofi, and has received institutional research funding from Sanofi and travel expenses from Astellas, Bristol-Myers Squibb, and Sanofi. H.M. and S.B.N. are former employees of and hold stock in Medivation. D.P. is an employee of Astellas Pharma. C.N.S. has received institutional research funding or honoraria from Astellas, Bayer, Cougar Biotechnology (now Janssen Oncology), Medivation, Sanofi, Genzyme, Ipsen, and Roche/Genentech. B.T. has received grants from Astellas, Ferring, and Sanofi, personal fees from Astellas, Bayer, Ferring, Medivation, and Sanofi, and nonfinancial support from Astellas.

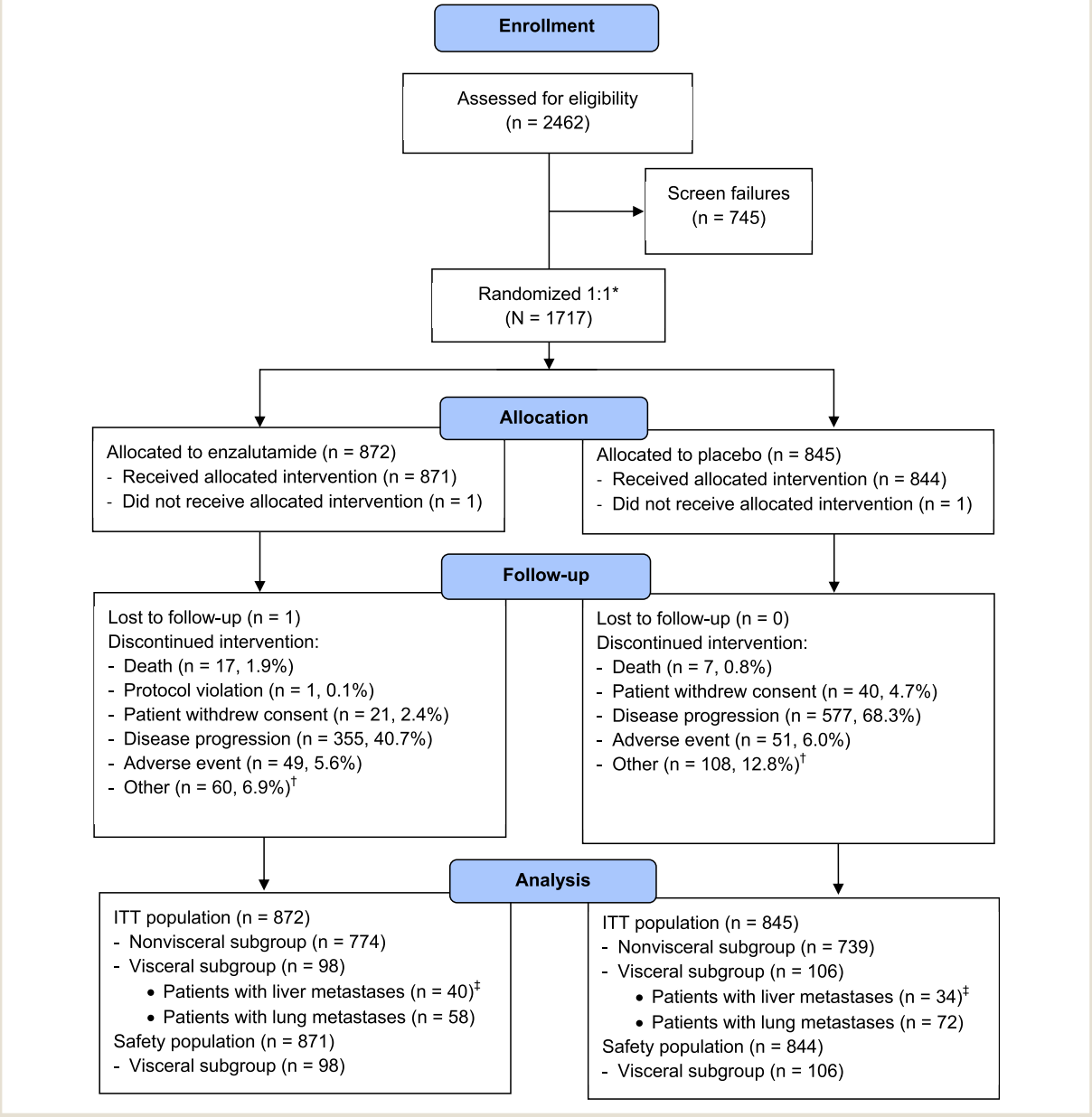
Supplemental Data

Supplemental table and figures accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.clgc.2017.02.007.

References

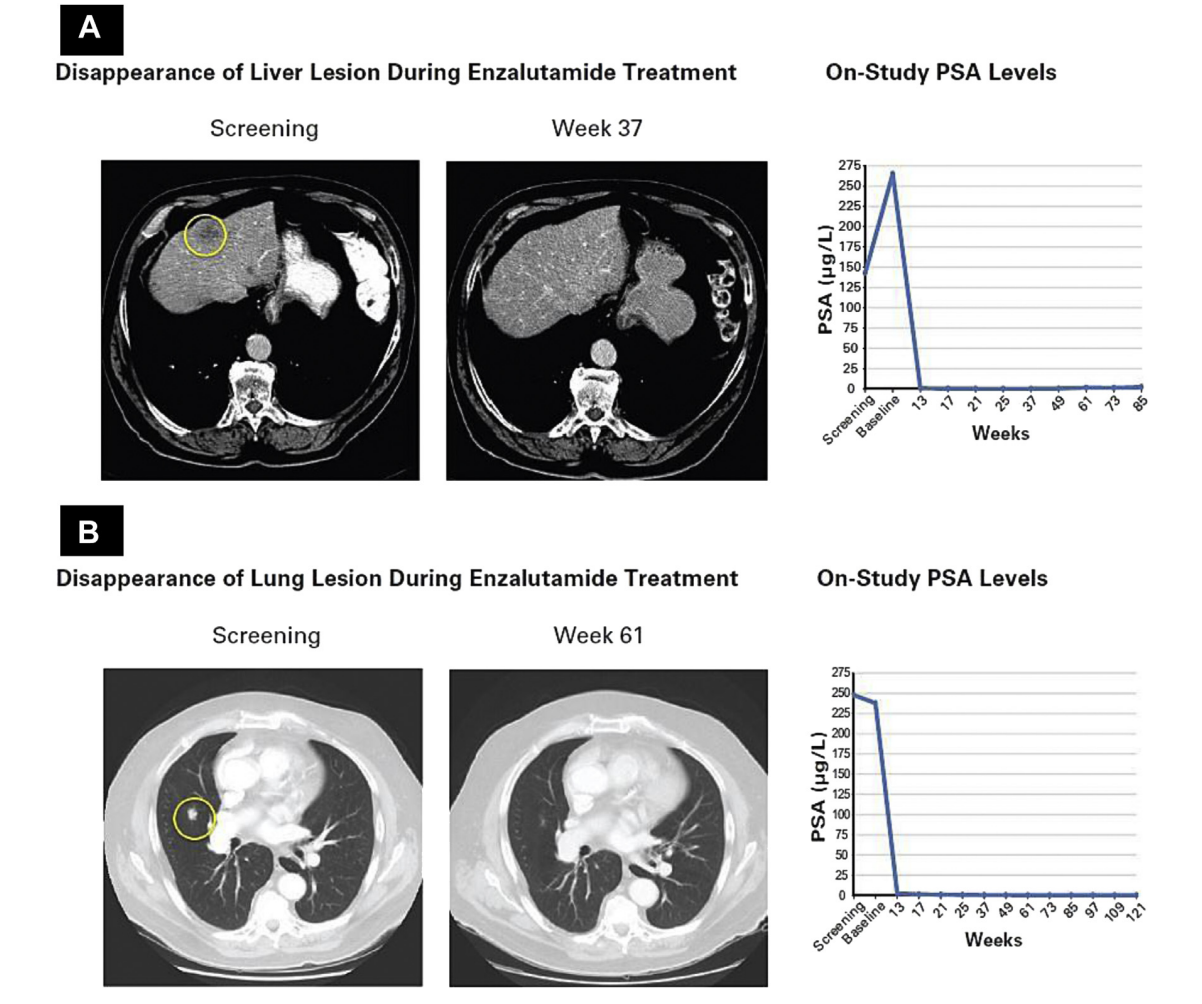
1. Cookson MS, Roth BJ, Dahm P, et al. Castration-resistant prostate cancer: AUA Guideline. *J Urol* 2013; 190:429-38.
2. Kirby M, Hirst C, Crawford ED. Characterising the castration resistant prostate cancer population: a systematic review. *Int J Clin Pract* 2011; 65:1180-92.
3. Halabi S, Lin CY, Kelly WK, et al. Updated prognostic model for predicting overall survival in first-line chemotherapy for patients with metastatic castration-resistant prostate cancer. *J Clin Oncol* 2014; 32:671-7.
4. Pond GR, Sonpavde G, de Wit R, Eisenberger MA, Tannock IF, Armstrong AJ. The prognostic importance of metastatic site in men with metastatic castration-resistant prostate cancer. *Eur Urol* 2014; 65:3-6.
5. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med* 2014; 371:424-33.
6. Rathkopf DE, Smith MR, de Bono JS, et al. Updated interim efficacy analysis and long-term safety of abiraterone acetate in metastatic castration-resistant prostate cancer patients without prior chemotherapy (COU-AA-302). *Eur Urol* 2014; 66:815-25.
7. American Cancer Society. Cancer Statistics Center, 2016 estimates, Available at: https://cancerstatisticscenter.cancer.org/?_ga=1.71728218.897263895.1448059162#/. Accessed: November 21, 2016.
8. Goodman OB Jr, Flaig TW, Molina A, et al. Exploratory analysis of the visceral disease subgroup in a phase III study of abiraterone acetate in metastatic castration-resistant prostate cancer. *Prostate Cancer Prostatic Dis* 2014; 17:34-9.
9. Loriot Y, Fizazi K, de Bono JS, Forer D, Hirmand M, Scher HI. Outcomes in patients with liver or lung metastatic castration-resistant prostate cancer (mCRPC) treated with the androgen receptor inhibitor enzalutamide: results from the phase III AFFIRM trial. *J Clin Oncol* 2013; 31(suppl 15), abstract 5065.
10. Tannock IF, de Wit R, Berry WR, et al, TAX 327 Investigators. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004; 351:1502-12.
11. Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med* 2004; 351:1513-20.
12. Scher HI, Fizazi K, Saad F, et al, AFFIRM Investigators. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med* 2012; 367:1187-97.
13. de Bono JS, Logothetis CJ, Molina A, et al, COU-AA-301 Investigators. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med* 2011; 364:1995-2005.
14. de Bono JS, Oudard S, Ozguroglu M, et al, TROPIC Investigators. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet* 2010; 376:1147-54.
15. Ryan CJ, Smith MR, de Bono JS, et al, COU-AA-302 Investigators. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med* 2013; 368:138-48.
16. Kantoff PW, Higano CS, Shore ND, et al, IMPACT Study Investigators. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med* 2010; 363:411-22.
17. Evans CP, Higano CS, Keane T, et al. The PREVAIL study: primary outcomes by site and extent of baseline disease for enzalutamide-treated men with chemotherapy-naïve metastatic castration-resistant prostate cancer. *Eur Urol* 2016; 70:675-83.
18. Berthold DR, Pond GR, Soban F, de Wit R, Eisenberger M, Tannock IF. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. *J Clin Oncol* 2008; 26:242-5.
19. Scher HI, Halabi S, Tannock I, et al, Prostate Cancer Clinical Trials Working Group. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol* 2008; 26:1148-59.

Supplemental Figure 1 PREVAIL CONSORT Diagram



Abbreviation: ITT = intent-to-treat. *Randomization was stratified by study site. †Majority discontinued due to rising prostate-specific antigen. ‡Liver only or liver and lung metastases.

Supplemental Figure 2 Example of Complete Responses in Metastatic Castration-resistant Prostate Cancer Patients With a Liver Lesion (A) and Lung Lesion (B) at Baseline



Abbreviation: PSA = prostate-specific antigen.

Supplemental Table 1 Summary of AEs in the PREVAIL Visceral Subgroup (Liver and Lung Subsets Combined) and Full Population

Parameter	Visceral Subgroup, n (%)		Full Study Population, n (%)[a]	
	Enzalutamide (n = 98)	Placebo (n = 106)	Enzalutamide (n = 871)	Placebo (n = 844)
AE				
Any AE	94 (96)	98 (93)	844 (97)	787 (93)
Any grade 3-4 AE	47 (48)	38 (36)	374 (43)	313 (37)
Any serious AE	35 (36)	33 (31)	279 (32)	226 (27)
Most common AEs[b]				
Fatigue	28 (29)	26 (25)	310 (36)	218 (26)
Back pain	25 (26)	24 (23)	235 (27)	187 (22)
Constipation	26 (27)	20 (19)	193 (22)	145 (17)
Arthralgia	17 (17)	12 (11)	177 (20)	135 (16)
Specific AEs				
Hypertension	11 (11)	4 (3.8)	117 (13)	35 (4.1)
Cardiac AEs	12 (12)	7 (6.6)	88 (10)	66 (7.8)
Alanine aminotransferase elevation	2 (2.0)	2 (1.9)	8 (0.9)	5 (0.6)
Seizure	0	1 (0.9)	1 (0.1)[c]	1 (0.1)
AE, event rate per 100 patient-years of exposure				
Fatigue	28.8	50.0	29.9	43.0
Back pain	26.1	53.9	23.6	42.5
Constipation	25.3	40.4	18.5	28.4
Arthralgia	20.9	23.1	18.6	29.5
Hypertension	11.3	7.7	10.8	6.6
Cardiac disorders	19.2	15.4	10.3	14.8

Abbreviation: AE = adverse event.
[a]One patient in each treatment group was enrolled but never treated.
[b]At least 20% on enzalutamide and ≥ 2% more than placebo in the safety population.
[c]This seizure occurred after the data cutoff date.

VOLUME 36 · NUMBER 10 · APRIL 1, 2018

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Targeting Androgen Receptor and DNA Repair in Metastatic Castration-Resistant Prostate Cancer: Results From NCI 9012

Maha Hussain, Stephanie Daignault-Newton, Przemyslaw W. Twardowski, Costantine Albany, Mark N. Stein, Lakshmi P. Kunju, Javed Siddiqui, Yi-Mi Wu, Dan Robinson, Robert J. Lonigro, Xuhong Cao, Scott A. Tomlins, Rohit Mehra, Kathleen A. Cooney, Bruce Montgomery, Emmanuel S. Antonarakis, Daniel H. Shevrin, Paul G. Corn, Young E. Whang, David C. Smith, Megan V. Caram, Karen E. Knudsen, Walter M. Stadler, Felix Y. Feng, and Arul M. Chinnaiyan

Author affiliations and support information (if applicable) appear at the end of this article.

Published at jco.org on December 20, 2017.

Clinical trial information: NCT01576172.

Corresponding author: Maha Hussain, MD, 303 E. Superior St, Suite 3-107, Chicago, IL 60611; e-mail: maha.hussain@northwestern.edu.

0732-183X/18/3610w-991w/$20.00

ABSTRACT

Purpose

To determine whether cotargeting poly (ADP-ribose) polymerase-1 plus androgen receptor is superior to androgen receptor inhibition in metastatic castration-resistant prostate cancer (mCRPC) and whether ETS fusions predict response.

Patients and Methods

Patients underwent metastatic site biopsy and were stratified by ETS status and randomly assigned to abiraterone plus prednisone without (arm A) or with veliparib (arm B). Primary objectives were: confirmed prostate-specific antigen (PSA) response rate (RR) and whether ETS fusions predicted response. Secondary objectives were: safety, measurable disease RR (mRR), progression-free survival (PFS), and molecular biomarker analysis. A total of 148 patients were randomly assigned to detect a 20% PSA RR improvement.

Results

A total of 148 patients with mCRPC were randomly assigned: arm A, n = 72; arm B, n = 76. There were no differences in PSA RR (63.9% *v* 72.4%; $P = .27$), mRR (45.0% *v* 52.2%; $P = .51$), or median PFS (10.1 *v* 11 months; $P = .99$). ETS fusions did not predict response. Exploratory analysis of tumor sequencing (80 patients) revealed: 41 patients (51%) were ETS positive, 20 (25%) had DNA-damage repair defect (DRD), 41 (51%) had *AR* amplification or copy gain, 34 (43%) had *PTEN* mutation, 33 (41%) had *TP53* mutation, 39 (49%) had PIK3CA pathway activation, and 12 (15%) had WNT pathway alteration. Patients with DRD had significantly higher PSA RR (90% *v* 56.7%; $P = .007$) and mRR (87.5% *v* 38.6%; $P = .001$), PSA decline ≥ 90% (75% *v* 25%; $P = .001$), and longer median PFS (14.5 *v* 8.1 months; $P = .025$) versus those with wild-type tumors. Median PFS was longer in patients with normal *PTEN* (13.5 *v* 6.7 months; $P = .02$), *TP53* (13.5 *v* 7.7 months; $P = .01$), and PIK3CA (13.8 *v* 8.3 months; $P = .03$) versus those with mutation or activation. In multivariable analysis adjusting for clinical covariates, DRD association with PFS remained significant.

Conclusion

Veliparib and ETS status did not affect response. Exploratory analysis identified a novel DRD association with mCRPC outcomes.

J Clin Oncol 36:991-999. © 2017 by American Society of Clinical Oncology

INTRODUCTION

Despite a high response rate (RR) to androgen deprivation (AD), a majority of patients with metastatic prostate cancer (PCa) will experience progression to castration resistance. Advances in understanding the biology and progression mechanisms to castration resistance led to development and approval of novel androgen receptor (AR) –targeted therapies: abiraterone acetate plus prednisone (AAP) and enzalutamide.[1,2] Both prolong survival in metastatic castration-resistant prostate cancer (mCRPC) irrespective of prior docetaxel.[3,4] However, many patients exhibit de novo resistance to both therapies, and resistance invariably occurs in responders, warranting a search for better treatments.[5-8]

Several studies have shown that AR regulates components of DNA-repair pathways, and conversely, several enzymes involved in DNA repair can modulate AR activity.[9-15] An important example is

ASSOCIATED CONTENT

See accompanying article on page 1017

Appendix

DOI: https://doi.org/10.1200/JCO.2017.75.7310

DOI: https://doi.org/10.1200/JCO.2017.75.7310

poly (ADP-ribose) polymerase-1 (PARP1), an enzyme with essential roles in recognition and repair of single-strand DNA breaks through base excision repair process.[16] Several cancers, including CRPC, exhibit increased PARP1 expression and/or activity.[16-19] Compelling data implicate PARP1 in mediation of DNA-repair responses to alkylators, cellular survival in BRCA-deficient cells, and AR-mediated PCa cell proliferation.[16,20-23] Specifically, preclinical studies using PARP1 inhibitors (eg, veliparib, olaparib) in PCa showed that PARP1 activity was required for maximal AR function.[16] In vivo, PARP1 inhibition with veliparib was as effective as castration in preventing tumor growth, and even greater inhibition was achieved with combination veliparib and castration.[16]

Canonic ETS gene fusions (androgen-responsive promoters driving ETS transcription factor overexpression) are present in > 50% of patients with PCa. ERG, the predominant ETS gene fusion product, physically interacts with PARP1.[24-26] PARP1 is required for full ERG activity and its downstream oncogenic functions. ERG-positive xenografts are preferentially sensitive to PARP1 inhibitors.[26]

On the basis of these data, we hypothesized that in patients with mCRPC, cotargeting AR and PARP1 would result in a better RR than AAP and the combination would be most effective in patients with ETS fusion–positive tumors.

PATIENTS AND METHODS

Patients

Eligible patients had mCRPC, Eastern Cooperative Oncology Group performance status of 0 to 2, testosterone < 50 ng/dL, normal organ function, no prior exposure to AAP, and up to two prior chemotherapy regimens. Complete eligibility criteria are outlined in the Study Protocol. All patients provided written informed consent per institutional and federal guidelines.

Study Design, Treatment, and End Points

This was a biomarker-stratified and randomized phase II multicenter trial (Fig 1). The primary objectives were to evaluate whether AAP plus veliparib is superior to AAP, as reflected by prostate-specific antigen (PSA)

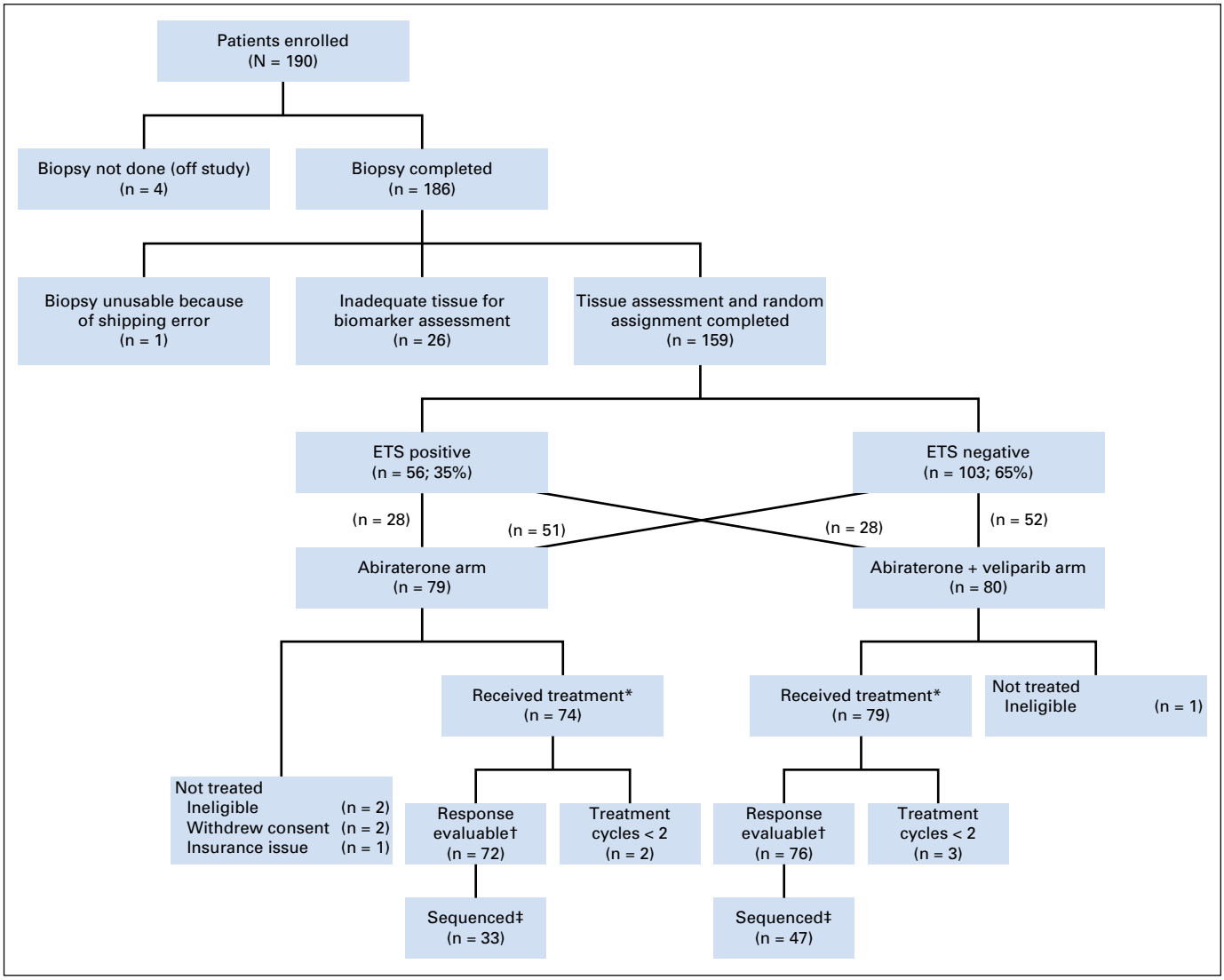


Fig 1. CONSORT diagram. (*) Safety evaluable. (†) Defined as having received two cycles of therapy or removed because of toxicity; five patients who received < two cycles did so by patient choice. (‡) Sequencing completed for all patients with sufficient extra tissue from biopsy required for sequencing.

RR (≥ 50% decline), and whether ETS gene fusion predicts response. Other end points included measurable disease RR (mRR), progression-free survival (PFS), toxicities, and exploratory tumor molecular analysis.

All patients underwent metastatic disease biopsy (unless metastatic archival tissue was available). ETS status was determined by immunohistochemistry (IHC) for ERG and in situ hybridization (ISH) –based assays for ETV1 fusions,[27,28] conducted in a College of American Pathologists/Clinical Laboratory Improvement Amendments–accredited laboratory. The study was activated before AAP approval in prechemotherapy setting. Eligible patients were stratified by prior ketoconazole and ETS fusion status (positive or negative) and randomly assigned to AA 1,000 mg per day plus prednisone 5 mg twice per day (arm A) or AAP plus veliparib 300 mg twice per day (arm B), for days 1 to 28. Arm B patients underwent lead-in treatment with AAP, followed on day 8 by veliparib, in cycle 1 only. Treatment was continued until radiographic/clinical disease progression, intercurrent illness, unacceptable adverse events (AEs), withdrawal of consent, or death.

Assessments

Patients underwent baseline disease assessments and then every 12 weeks with bone scan, computed tomography or magnetic resonance imaging of abdomen/pelvis, and x-ray or computed tomography of chest for the first year. For patients who have completed ≥ 1 year of therapy, imaging can be done every 4 months, and for patients who have completed ≥ 2 years of therapy, imaging can be done every 6 months. Irrespective of duration on therapy, imaging can be done sooner than the specified intervals as clinically indicated. PSA was assessed at baseline and on day 1 of each cycle. AEs were graded according to Common Terminology Criteria for Adverse Events (version 4.0).

Tumor Sequencing

Extra tumor tissue for sequencing was available for 87 patients; 80 of 87 were response evaluable (four patients received < two cycles of treatment, three patients were never treated, one was ineligible, and two withdrew consent). Their baseline characteristics are detailed in Appendix Tables A1 and A2 (online only). Flash-frozen biopsies were processed for genomic DNA and total RNA isolation using Qiagen AllPrep Kit (Hilden, Germany) and then underwent targeted exon sequencing and capture transcriptome analysis at University of Michigan (Ann Arbor, MI), as previously detailed.[29,30]

Statistical Analysis

Biomarker-stratified design[31] was used to determine a PSA RR difference between arms A and B and between arms by ETS fusion (positive *v* negative strata). The trial was designed to accrue 148 response-evaluable patients randomly assigned at a one-to-one ratio to arms A and B to provide 80% power at a one-sided 5% significance level to detect an improvement of 20% in PSA RR between arms with a χ^2 test of proportions, assuming a PSA RR of 30% in arm A (based on data available at time of study design).[1] Response-evaluable patients were those receiving at least two therapy cycles or those removed from study because of toxicity before completing two cycles. The PSA RR difference between treatment groups by ETS fusion status was an interaction test with a significance threshold of .15 from a logistic model (trial design details provided in protocol).

The primary outcome of confirmed PSA RR (complete or partial response) was analyzed with χ^2 tests to test differences between treatment arms and differences within a biomarker stratum between treatment arms. Confirmed PSA RR was modeled to test ETS fusion status as prognostic using a logistic model with ETS status as the only covariate and as predictive using logistic models testing interaction of treatment arm and ETS. Similar models were used for mRR. Both prognostic and predictive models were used in the exploratory analyses for each sequencing biomarker including DNA-damage repair defect (DRD). Secondary end point PFS was reported using Kaplan-Meier methods and associated log-rank tests. Exploratory analysis for prognostic biomarkers with association with PFS was reported using product-limit estimates and log-rank tests. Cox models were used to test biomarkers as predictive of PFS with models including an interaction of treatment arm and biomarker status. An unplanned analysis using a multivariable Cox model for PFS was used to explore biomarker associations with PFS after controlling for clinical covariates by adding the biomarker to the model including the clinical covariates. Each biomarker was modeled separately. All analyses were completed using SAS software (version 9.4; SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

From May 2012 through December 2015, 190 patients with mCRPC were enrolled at 12 centers (Table 1); 185 eligible patients underwent metastatic biopsy (soft tissue, n = 89; bone, n = 96); 159

Table 1. Baseline Patient Demographic and Clinical Characteristics by Treatment Arm

Characteristic	No. (%)		*P*
	Arm A: Abiraterone (n = 74)	Arm B: Abiraterone + Veliparib (n = 79)	
Age, years			.35
Median	69	68	
Range	50-90	47-85	
Race			.09
White	61 (82.4)	74 (93.7)	
Black	9 (12.2)	3 (3.8)	
Other	4 (3.4)	2 (2.5)	
Performance status			.93
0	46 (62.2)	50 (63.3)	
1	28 (37.8)	28 (35.4)	
2	0	1 (1.3)	
PSA, ng/mL			.67
Median	32.7	36.4	
Range	0.8-1,557.6	0.04-1,074.4	
Cancer pain present	23 (31.1)	26 (33.0)	.81
Sites of disease			
Bone	64 (86.5)	68 (86.1)	.94
Lymph node	45 (60.8)	53 (67.1)	.42
Visceral	13 (17.6)	21 (26.6)	.18
Other	13 (17.6)	16 (20.3)	.67
Previous treatments			
Chemotherapy	16 (20.8)	23 (30.3)	.29
Docetaxel/cabazitaxel	11 (14.9)	17 (21.5)	
Other	5 (6.8)	6 (7.6)	
Enzalutamide	2 (2.7)	2 (2.5)	.99
Sipuleucel-T	22 (29.7)	13 (16.5)	.05
Experimental agent	19 (25.7)	15 (19.0)	.32
Strata: ETS fusion and ketoconazole use			.83
ETS fusion positive*	25 (33.8)	28 (35.4)	
ETS fusion negative	49 (66.2)	51 (64.6)	
Previous ketoconazole	8 (10.8)	9 (11.3)	.91
No. of treatment cycles			.68
Median	9	9	
Range	1-46	1-50	
Overall survival			—
Median	30.6	32.3	
95% CI	28.4 to NR	28.4 to NR	

Abbreviations: NR, not reached; PSA, prostate-specific antigen.
*ETS fusion determined by immunohistochemistry/in situ hybridization.

patients (86%) had adequate tissue; 35% were ETS positive; 153 patients (white, 88%; black, 8%; median age, 68 years; median PSA, 35.4 ng/mL) were randomly assigned to arm A (AAP; n = 74) or arm B (AAP + veliparib; n = 79; Fig 1).

Safety

Because of bothersome low-grade AEs, veliparib dose was reduced to 200 mg twice per day for cycle 1, and if tolerated, dose was escalated to 300 mg twice per day for subsequent cycles. Distribution of grade ≥ 3 AEs irrespective of attribution was similar between arms. Overall, therapy was well tolerated (Appendix Table A3, online only); hyperglycemia was the only high-grade treatment-related AE that occurred in > 5% of patients in either arm (arm A, 9%; arm B, 5%). In arm A, 20% of patients (n = 15) had grade 3 treatment-related AEs, and one patient had grade 4 hyperglycemia. In arm B, 24% of patients (n = 19) had grade 3 treatment-related AEs, one patient had grade 4 thrombocytopenia, and one patient had grade 5 cardiac arrest possibly treatment related. Any-grade AEs that were significantly more frequent ($P < .05$) in arm B versus arm A were fatigue, lymphopenia, nausea, and vomiting; edema occurred more frequently in arm A than arm B.

Efficacy

Of the 153 randomly assigned and treated patients, 148 were response evaluable; five (3%) were not evaluable (four patients chose to stop treatment within one cycle, and one had > 4-week treatment delay). There was no statistically significant difference between arms in confirmed PSA RR (arm A, 63.9%; arm B, 72.4%; $P = .27$), mRR (arm A, 45.0%; arm B, 52.2%; $P = .51$), or median PFS (arm A, 10.1 months; arm B, 11 months; $P = .99$; Table 2; Appendix Fig A1A). Furthermore, ETS fusion status did not predict PSA, mRR, or PFS (Appendix Fig A1B).

DRD and Additional Prognostic Biomarkers

For 87 patients, extra biopsy tumor tissue was analyzed by next-generation sequencing; 80 of 87 were treated and response evaluable (arm A, n = 33; arm B, n = 47). Sequenced patients' characteristics compared with those of patients who did not have tumor sequencing and their baseline characteristics by treatment arm are listed in Appendix Tables A1 and A2. Overall, the groups were fairly comparable, except for site of disease (bone *v* soft tissue [eg, lymph node, visceral disease]), which affected the site of biopsy: in the sequenced cohort, a majority (75%) were soft tissue biopsies, whereas in the nonsequenced population, a majority (70%) had bone biopsies. This is not surprising, considering tumor yield is known to be better with soft tissue biopsy. The tumor yield likely affected the difference between the two groups in the proportion of patients with ETS-positive tumors, which was higher in the sequenced group.

ETS fusion status was also analyzed by sequencing to evaluate concordance with the IHC/ISH methods used. Agreement between methods was observed for 72 (90%) of 80 patients (Appendix Table A4, online only); 41 patients (51.3%) were ETS positive by sequencing.

Sequencing classified patients into three categories of DNA-repair status (Fig 2A): wild type (WT; n = 55 [68.75%]), biallelic DRD (n = 20 [25%]), and monoallelic DRD (n = 5 [6.25%]). Patients with DRD had alterations in *BRCA1*, *BRCA2*, *ATM*, *FANCA*, *PALB2*, *RAD51B*, or *RAD51C*, with *BRCA2* being the most frequently detected (Fig 2A). Notably, these genes represent major players in the homologous recombination (HR) pathway, which functions along with the nonhomologous end-joining (NHEJ) pathway to repair DNA double-strand breaks.[15] Additional genes of interest were also significantly altered, including *AR* (n= 41 [51%]), *TP53* (n = 33 [41%]), *PTEN* (n = 34 [42.5%]), and *PIK3CA* (n = 39 [49%]). Alterations were also annotated for AR-related genes and the WNT pathway.

Table 2. Detailed PSA and Measurable Response Outcomes by Treatment Arm and ETS Gene Fusion Status

	Overall (n = 148)			ETS Positive (n = 52)			ETS Negative (n = 96)			
	No. (%)			No. (%)			No. (%)			
Response	Abiraterone	Abiraterone + Veliparib	*P*	Abiraterone	Abiraterone + Veliparib	*P*	Abiraterone	Abiraterone + Veliparib	*P*	Interaction *P*
PSA outcomes	(n = 72)	(n = 76)		(n = 25)	(n = 27)		(n = 47)	(n = 49)		
PSA response (CR/PR)	46 (63.9)	55 (72.4)	.27	15 (60.0)	19 (70.4)	.43	31 (66.0)	36 (73.5)	.42	.89
CR	12 (16.7)	12 (15.8)		4 (16.0)	3 (11.1)		8 (17.0)	9 (18.4)		
PR	34 (47.2)	43 (56.6)		11 (44.0)	16 (59.3)		23 (48.9)	27 (55.1)		
Stable disease	19 (26.4)	15 (19.7)		7 (28.0)	7 (25.9)		12 (25.5)	8 (16.3)		
Progressive disease	7 (9.7)	6 (7.9)		3 (12.0)	1 (3.7)		4 (8.5)	5 (10.2)		
Measurable disease	(n = 40)	(n = 46)		(n = 15)	(n = 19)		(n = 25)	(n = 27)		
RECIST response (CR/PR)	18 (45.0)	24 (52.2)	.51	6 (40.0)	10 (52.6)	.46	12 (48.0)	14 (51.9)	.78	.69
CR	1 (2.5)	0 (0)		0 (0)	0 (0)		1 (4.0)	0 (0)		
PR	17 (42.5)	24 (52.2)		6 (40.0)	10 (52.6)		11 (44.0)	14 (51.9)		
Stable disease	14 (35.0)	12 (26.1)		5 (33.3)	6 (31.6)		9 (36.0)	6 (22.2)		
Progressive disease	8 (20.0)	8 (17.4)		4 (26.7)	3 (15.8)		4 (16.0)	5 (18.5)		
Not evaluable	0 (0)	2 (4.4)		0 (0)	0 (0)		0 (0)	2 (7.4)		

Abbreviations: CR, complete response; PR, partial response; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors.

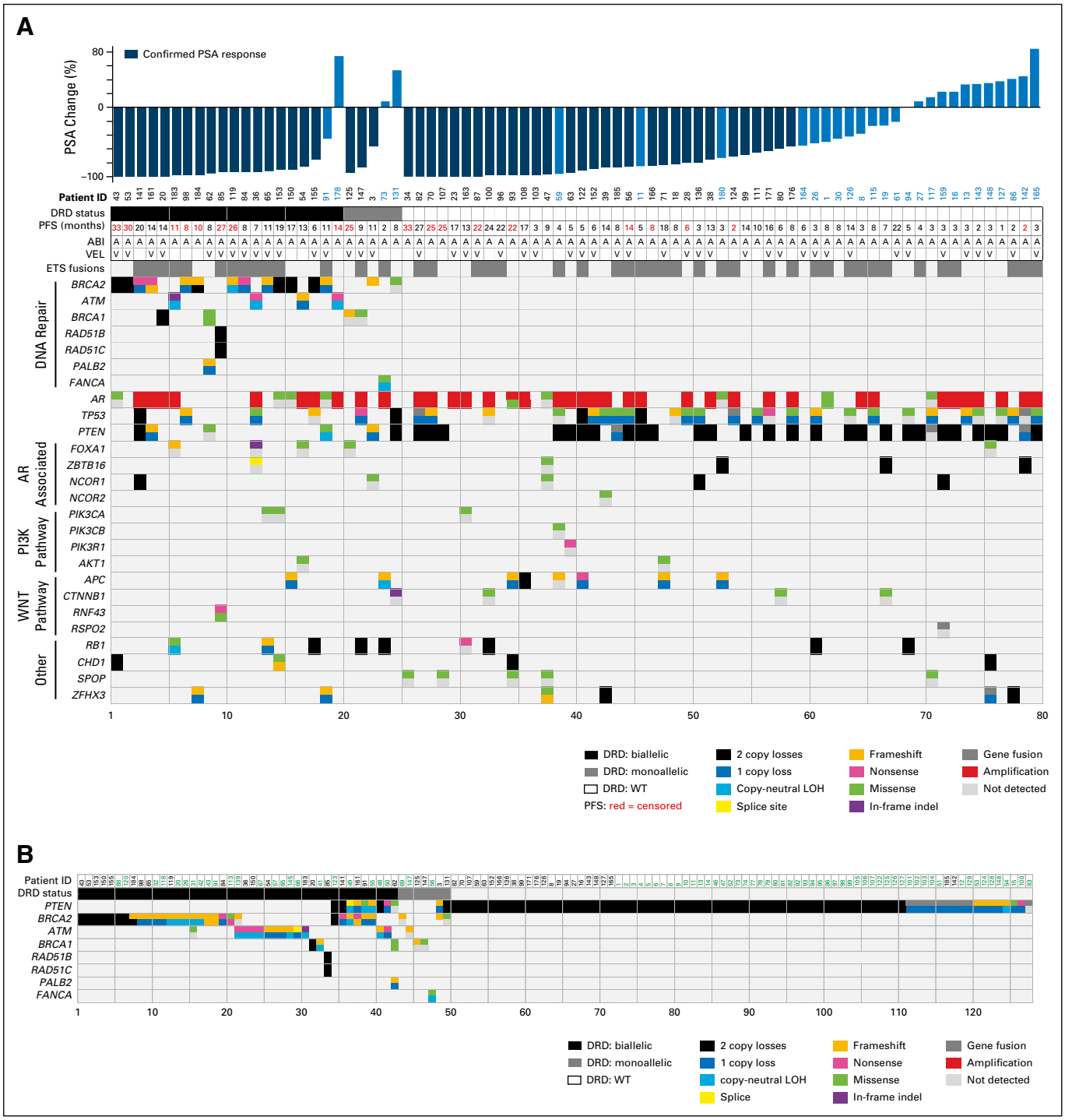


Fig 2. Landscape of molecular alterations, DNA-repair status, and survival in this cohort of patients with metastatic castration-resistant prostate cancer (mCRPC). (A) Next-generation sequencing of tumor tissues identified alterations in different genes for each patient (n = 80) as depicted in the matrix, called by each allele. Three groups of patients were determined based on DNA-damage repair defect (DRD) status, represented at the top by black (biallelic DRD), gray (monoallelic DRD), or white boxes (wild-type [WT] DRD). Above this, maximum percent decreases in prostate-specific antigen (PSA) levels throughout treatment are graphed for each patient, and those with confirmed PSA responses are noted with dark blue bars. Progression-free survival (PFS; months), treatment (abiraterone [A/ABI], veliparib [V/VEL]), and ETS fusion status are also indicated at the top of the matrix for each patient. (B) Matrix of DRD status associated with *PTEN* alterations. Patients along the top in black correspond to patients in this study, and patients in green represent cases from an additional mCRPC cohort.[29] (C) PFS curves are shown for patients with WT/monoallelic or biallelic DRD status. LOH, loss of heterozygosity.

Outcome analysis combined WT and monoallelic DRD patients, because the DRD status of the latter group is considered nondeleterious, and compared them with biallelic DRD patients. Prognostic covariates (metastatic site, performance status, PSA, pain, and prior therapies) were similar between DRD and WT groups except for prior sipuleucel-T therapy (DRD, n = 1 [5%] *v* WT, n = 16 [29%]).

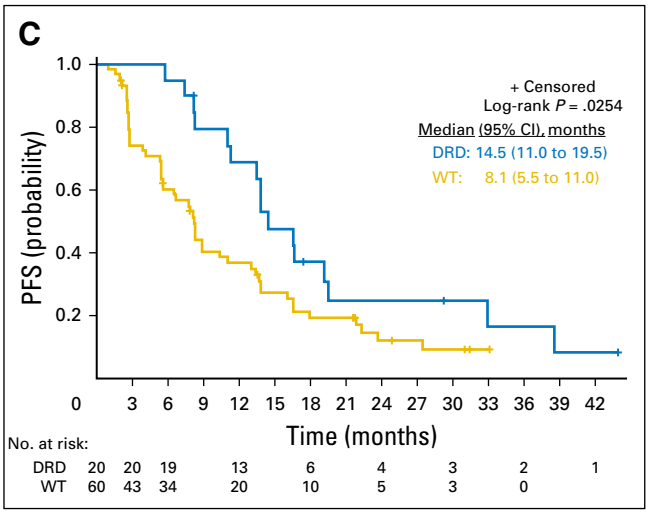


Fig 2. (Continued).

Unexpectedly, we uncovered a novel, significant association between DRD and overall outcome/response. Patients with DRD tumors had significantly higher confirmed PSA RR (90% *v* 56.7%; $P = .007$; Table 3; Fig 2A), PSA decline of ≥ 90% (75% *v* 25%; $P = .001$; Appendix Fig A2, online only), mRR (87.5% *v* 38.6%; $P = .001$; Table 3), and median PFS (14.5 *v* 8.1 months; $P = .025$; Fig 2C; depicted by treatment arm in Fig 3) compared with patients with WT tumors.

Analysis of Clinical and Molecular Variables

Exploratory biomarker analysis revealed three additional biomarkers associated with longer median PFS (Appendix Tables A5 and A6, online only). Significantly better overall outcomes were identified in patients with normal *PTEN* (13.5 *v* 6.7 months in those with mutation; $P = .02$), normal *TP53* (13.5 *v* 7.7 months in those with mutation; $P = .01$), or nonactivated PIK3CA pathway (13.8 *v* 8.3 months in those with activation; $P = .03$; Appendix Table A5, online only). Multivariable analysis including clinical and biomarker variables individually revealed DRD and TP53 as biomarkers separately associated with PFS after controlling for clinical covariates (Table 4). We also noted that mutation or loss of *PTEN* seemed to be almost mutually exclusive with DRD (Fig 2A).

Exceptional Responders

Several patients had exceptional and durable responses to therapy. These were patients in either arm with PFS > 24 months and PSA decline > 90%. On the basis of these criteria, 19 exceptional responders (arm A, n = 8; arm B, n = 11) were identified; their characteristics are listed in Appendix Table A7 (online only). Nine of 19 had tumor sequencing: four had biallelic DRD, one had monoallelic DRD, and four had WT tumors (Fig 2A; Appendix Table A8, online only).

DISCUSSION

This prospective metastatic tissue–based biomarker-stratified trial stratified patients with mCRPC by ETS fusion status and then randomly assigned them to AAP with or without veliparib. Preclinical data suggested that targeting PARP1 would synergize with AR inhibition, and ETS fusion–positive tumors would be preferentially sensitive to PARP1 inhibition.[13,16,26] However, the addition of veliparib did not affect response, nor did ETS status predict response. There was no difference between arms in the rate of exceptional responders (AAP, n = 8; AAP + veliparib, n = 11). ETS fusion concordance between IHC/ISH and sequencing was 90%. ERG/ETS failure to predict response may have been a result of the high prevalence of defects in DRD genes (approximately 25% of patients), which was not known at time of study design.

Exploratory metastatic tissue sequencing analysis uncovered a novel finding. Several patients had alterations in genes involved in DNA repair, particularly those implicated in the HR pathway; DRD was significantly associated with better response and PFS irrespective of treatment arm. Prior studies demonstrated mechanistic connections between AR and DNA repair in prostate cancer models,[9-15] but ours is the first report, to our knowledge, to show the association of DRD with outcome in patients with mCRPC treated with AAP with higher PSA RR, mRR, and PFS compared with patients with WT tumors. However, additional studies are needed for confirmation, because this trial was not designed specifically to test DRD predictive power with AR-targeted therapy. A recent trial in mCRPC showed that DRD was associated with high RRs to a different PARP1 inhibitor (olaparib), but there was no control arm of an AR-targeted agent.[32]

Table 3. PSA and Measurable Disease Response Rate by DNA Repair Status

	Prognostic Biomarker			DRD (n = 20)			DNA-Repair WT/Monoallelic (n = 60)			
	No. (%)			No. (%)			No. (%)			
Response	DRD	DNA-Repair WT/ Monoallelic	*P*	Abiraterone	Abiraterone + Veliparib	*P*	Abiraterone	Abiraterone + Veliparib	*P*	Interaction *P*
PSA	(n = 20)	(n = 60)		(n = 7)	(n = 13)		(n = 26)	(n = 34)		
PSA response	18 (90.0)	34 (56.7)	.007	6 (85.7)	12 (92.3)	1.0	12 (46.2)	22 (64.7)	.15	.97
95% CI, %	76.9 to 100	44.1 to 69.2		59.8 to 100	77.8 to 100		27.0 to 65.3	48.6 to 80.8		
Measurable disease	(n = 16)	(n = 44)		(n = 5)	(n = 11)		(n = 19)	(n = 25)		
RECIST response	14 (87.5)	17 (38.6)	.001	4 (80.0)	10 (90.9)	1.0	7 (36.8)	10 (40.0)	.83	.64
95% CI, %	59.5 to 98.3	24.1 to 54.0		44.9 to 100	73.9 to 100		15.2 to 58.5	20.8 to 59.2		

Abbreviations: DRD, DNA-damage repair defect; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors; WT, wild type.

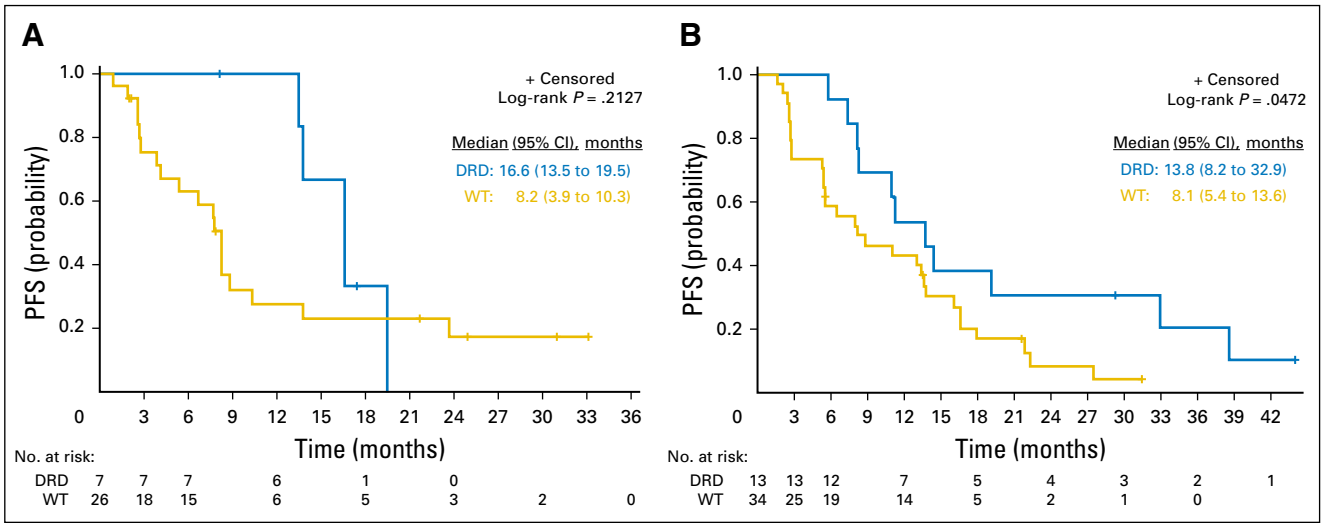


Fig 3. Survival by DNA-repair status and treatment arm. Progression-free survival (PFS) curves are shown by treatment arm for patients with wild-type (WT)/monoallelic or biallelic DNA-damage repair defect (DRD), as determined by next-generation sequencing of tumors shown in Figure 2 of the main manuscript: (A) abiraterone/prednisone; (B) abiraterone/prednisone plus veliparib.

AR plays a major role in promoting double-strand DNA break repair.[12,13] As such, AR blockade alone would be expected to compromise DNA repair. This concept is supported by our data, wherein tumors defective in DNA repair were sensitized to AAP. Given this recently realized redundancy in function (eg, capacity of both PARP1 inhibitors and AR blockade to suppress DNA repair), it is not unexpected that PARP1 inhibitors did not add to AR blockade.

Our results also raise the question of how DNA repair alterations may be associated with better outcomes with AR-targeted therapy. Recent studies have shown that AR directly regulates genes involved in DNA-damage responses that allow prostate cancer cells to enhance DNA repair, decrease DNA damage, and continue cycling.[10,12,13,15] Conversely, castration or treatment with antiandrogens leads to decreased expression of DNA-repair enzymes and therefore increased DNA damage and decreased cellular survival; in particular, inhibition of AR signaling has been shown to inhibit the expression of genes primarily involved in the NHEJ pathway of double-strand DNA break repair.[11-14] Disruption of NHEJ in the context of an underlying HR defect (the alterations identified in this trial cohort) could induce a synthetic lethality via disruption of both of the major repair pathways for double-stranded DNA breaks, thus explaining why patients with HR deficiencies fare better with AAP treatment. Furthermore, as described in this report, AR directly increases DNA-damage response effectors, and in turn, many DNA-damage response proteins directly modulate AR activity, including BRCA1 and BRCA2, two HR factors altered in several of the DRD patients.[33,34] Without functional BRCA1 or BRCA2 cofactors, it can be hypothesized that these patients may have had altered AR transcriptional activity compared with WT patients. Further analysis of the sequencing data herein uncovered a positive association with outcome for patients with normal expression of *PTEN* and *TP53* or nonactivated

Table 4. Multivariable Analysis of PFS by Biomarker Status (n = 80)

	Marker Status					Cox Model	
	Not Normal		Normal			Univariable	Multivariable*
Biomarker	No. (%)	Median PFS (months) (95% CI)	No. (%)	Median PFS (months) (95% CI)	Log-Rank *P*	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
DRD *v* WT/monoallelic	20 (25)	14.5 (11.0 to 19.5)	55 (69)	8.0 (5.4 to 13.0)	.02	0.52 (0.29 to 0.93)	0.51 (0.27 to 0.97)
TP53 (mutated *v* normal)	33 (41)	7.7 (5.3 to 8.8)	47 (59)	13.5 (8.2 to 16.6)	.01	1.88 (1.14 to 3.12)	2.52 (1.30 to 4.89)
PTEN (mutated *v* normal)	34 (43)	6.7 (4.1 to 11.3)	46 (57)	13.5 (8.2 to 16.6)	.02	1.82 (1.11 to 3.01)	1.61 (0.92 to 2.82)
PIK3CA (activated *v* normal)	39 (49)	8.3 (5.4 to 13.3)	41 (51)	13.8 (8.2 to 16.6)	.03	1.74 (1.05 to 2.87)	1.45 (0.79 to 2.68)
SPOP (mutated *v* normal)	5 (6)	NR (2.8 to NR)	75 (94)	8.8 (7.8 to 13.6)	.06	0.28 (0.07 to 1.15)	0.54 (0.09 to 3.40)
CHD1 (mutated *v* normal)	4 (5)	NR (2.6 to NR)	76 (95)	8.8 (7.8 to 13.6)	.09	0.31 (0.07 to 1.29)	0.39 (0.09 to 1.71)
AR (amplified/mutated *v* normal)	41 (51)	8.8 (5.4 to 13.5)	39 (49)	11.0 (8.0 to 16.6)	.17	1.41 (0.86 to 2.31)	1.34 (0.80 to 2.23)
ZFHX3 (mutated *v* normal)	6 (8)	10.0 (2.1 to 13.8)	74 (92)	10.3 (8.0 to 13.8)	.20	1.74 (0.74 to 4.09)	1.44 (0.57 to 3.63)
RB1 (mutated *v* normal)	9 (11)	8.8 (1.9 to 23.7)	71 (89)	10.3 (8.0 to 13.8)	.46	1.32 (0.62 to 2.78)	1.47 (0.66 to 3.28)
ETS (positive *v* negative)	41 (51)	8.2 (5.4 to 14.5)	39 (49)	13.3 (8.2 to 13.8)	.48	1.19 (0.73 to 1.95)	1.24 (0.45 to 3.38)
WNT (activated *v* normal)	12 (15)	12.4 (2.7 to 23.7)	68 (85)	10.3 (8.0 to 13.6)	.91	0.96 (0.5 to 1.85)	0.88 (0.44 to 1.74)

Abbreviations: DRD, DNA-damage repair defect; NR, not reached; PFS, progression-free survival; WT, wild type.
*Multivariable model includes age, baseline prostate-specific antigen, race, Eastern Cooperative Oncology Group performance status, treatment arm, prior chemotherapy, prior ketoconazole, fusion status stratum, and biomarker of interest.

PIK3CA pathway. However, multivariable analysis including clinical and biomarker variables individually revealed DRD and TP53 as biomarkers separately associated with PFS after controlling for clinical covariates. Expanded analysis of DRD and *PTEN* from an additional mCRPC cohort[29] demonstrated that DRD patients had significantly less aberrations in *PTEN*, whereas patients with WT DNA repair all had *PTEN* loss or aberration. The mutual exclusivity between DRD and *PTEN* could further explain why patients with WT DNA repair had worse outcome with therapy. *PTEN* loss has been associated with more aggressive prostate cancers, and preclinical models have suggested that *PTEN* loss/PIK3CA pathway activation can alter AR transcriptional activity and lead to hormonal therapy resistance.[35,36] Directly related to our results, in retrospective analyses of patients with mCRPC receiving AAP in the postdocetaxel setting, *PTEN* loss was associated with shorter overall survival from time of initiation of AAP treatment.[37]

In contrast to findings presented here, a recent study proposed that patients with germline DRD have decreased time from androgen-deprivation therapy initiation to castration resistance and worse outcome with first-line hormonal therapy once CRPC develops.[38] Important differences in these two studies are evident and could account for discrepancies. In our trial, DRD was determined by metastatic tumor tissue sequencing, the gold standard for detecting alterations. The contrasting study did not analyze tumor tissue but rather defined DRD through targeted germline sequencing. The WT DNA repair patients with whom the DRD patients were compared were only classified as such through germline sequencing, thus not accounting for those WT germline patients who may have acquired somatic DRD events. Indeed, the authors proceeded to sequence cell-free DNA, but only from those patients who were first determined to have germline DRD; these patients totaled 21 in comparison with the 80 tumors sequenced in our study. Finally, the patients with mCRPC in the previous study were treated with enzalutamide or AAP; in contrast, patients in our trial all received AAP.

There are several limitations in our study. The analyses of the biomarkers from sequencing were unplanned and exploratory and included a convenient sample of 80 of 148 patients who had extra biopsy tissue. The sequenced cohort included more soft tissue biopsies compared with patients who were not sequenced. This is not surprising, considering the known fact that the tissue yield is better from soft tissue metastases. The tumor tissue yield also likely affected the difference in the rate of ETS-positive tumors between the two cohorts. The multivariable modeling included many covariates for the sample size, so caution should be taken when interpreting these results. Additionally, there was not a correction for multiple comparisons in this study. Additional validation is needed for the exploratory findings.

In conclusion, this metastatic tissue biomarker-stratified, randomized trial in mCRPC showed that the approach is feasible. Despite robust preclinical supporting evidence, the addition of veliparib to AAP did not affect response, nor did ETS fusion predict response. Nonetheless, exploratory analysis led to the novel and unexpected finding that DRD was associated with improved outcomes with AAP treatment, possibly through induction of a synthetic lethality in the context of HR defects. Interestingly, DRD was also generally associated with normal PTEN status. Normal *PTEN*, normal *TP53*, and nonactivated PIK3CA signaling were significantly associated with improved outcome overall. These hypothesis-generating observations are being evaluated in a follow-up DRD-preselected randomized trial (AAP *v* olaparib *v* combination). These results highlight the complexity of mCRPC, importance of the totality of the biologic context, and need for informative clinical trial designs.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Maha Hussain, Stephanie Daignault-Newton, Karen E. Knudsen, Walter M. Stadler, Felix Y. Feng, Arul M. Chinnaiyan
Financial support: Maha Hussain, Walter M. Stadler, Arul M. Chinnaiyan
Administrative support: Maha Hussain, Walter M. Stadler
Provision of study materials or patients: Maha Hussain, Przemyslaw W. Twardowski, Costantine Albany, Mark N. Stein, Kathleen A. Cooney, Bruce Montgomery, Emmanuel S. Antonarakis, Daniel H. Shevrin, Paul G. Corn, Young E. Whang, David C. Smith, and Megan V. Caram, Walter M. Stadler
Collection and assembly of data: Maha Hussain, Przemyslaw W. Twardowski, Costantine Albany, Mark N. Stein, Javed Siddiqui, Robert J. Lonigro, Xuhong Cao, Scott A. Tomlins, Rohit Mehra, Bruce Montgomery, Emmanuel S. Antonarakis, Daniel H. Shevrin, Paul G. Corn, Young E. Whang, David C. Smith, Megan V. Caram, Walter M. Stadler
Data analysis and interpretation: Maha Hussain, Stephanie Daignault-Newton, Lakshmi P Kunju, Yi-Mi Wu, Dan Robinson, Emmanuel S. Antonarakis, Felix Y. Feng, Arul M. Chinnaiyan
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

REFERENCES

1. de Bono JS, Logothetis CJ, Molina A, et al: Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 364:1995-2005, 2011
2. Scher HI, Fizazi K, Saad F, et al: Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 367:1187-1197, 2012
3. Ryan CJ, Smith MR, de Bono JS, et al: Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 368:138-148, 2013
4. Beer TM, Armstrong AJ, Rathkopf DE, et al: Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 371:424-433, 2014
5. Antonarakis ES, Lu C, Wang H, et al: AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. N Engl J Med 371:1028-1038, 2014
6. Mostaghel EA, Marck BT, Plymate SR, et al: Resistance to CYP17A1 inhibition with abiraterone in castration-resistant prostate cancer: Induction of steroidogenesis and androgen receptor splice variants. Clin Cancer Res 17:5913-5925, 2011
7. Watson PA, Arora VK, Sawyers CL: Emerging mechanisms of resistance to androgen receptor inhibitors in prostate cancer. Nat Rev Cancer 15: 701-711, 2015
8. Korpal M, Korn JM, Gao X, et al: An F876L mutation in androgen receptor confers genetic and phenotypic resistance to MDV3100 (enzalutamide). Cancer Discov 3:1030-1043, 2013
9. Haffner MC, Aryee MJ, Toubaji A, et al: Androgen-induced TOP2B-mediated double-strand breaks and prostate cancer gene rearrangements. Nat Genet 42:668-675, 2010

10. Ta HQ, Gioeli D: The convergence of DNA damage checkpoint pathways and androgen receptor signaling in prostate cancer. Endocr Relat Cancer 21: R395-R407, 2014

11. Tarish FL, Schultz N, Tanoglidi A, et al: Castration radiosensitizes prostate cancer tissue by impairing DNA double-strand break repair. Sci Transl Med 7:312re11, 2015

12. Goodwin JF, Schiewer MJ, Dean JL, et al: A hormone-DNA repair circuit governs the response to genotoxic insult. Cancer Discov 3:1254-1271, 2013

13. Polkinghorn WR, Parker JS, Lee MX, et al: Androgen receptor signaling regulates DNA repair in prostate cancers. Cancer Discov 3:1245-1253, 2013

14. Al-Ubaidi FL, Schultz N, Loseva O, et al: Castration therapy results in decreased Ku70 levels in prostate cancer. Clin Cancer Res 19:1547-1556, 2013

15. Schiewer MJ, Knudsen KE: Linking DNA damage and hormone signaling pathways in cancer. Trends Endocrinol Metab 27:216-225, 2016

16. Schiewer MJ, Goodwin JF, Han S, et al: Dual roles of PARP-1 promote cancer growth and progression. Cancer Discov 2:1134-1149, 2012

17. Hirai K, Ueda K, Hayaishi O: Aberration of poly (adenosine diphosphate-ribose) metabolism in human colon adenomatous polyps and cancers. Cancer Res 43:3441-3446, 1983

18. Fukushima M, Kuzuya K, Ota K, et al: Poly(ADP-ribose) synthesis in human cervical cancer cell-diagnostic cytological usefulness. Cancer Lett 14:227-236, 1981

19. Tomoda T, Kurashige T, Moriki T, et al: Enhanced expression of poly(ADP-ribose) synthetase gene in malignant lymphoma. Am J Hematol 37:223-227, 1991

20. Farmer H, McCabe N, Lord CJ, et al: Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 434:917-921, 2005

21. Bryant HE, Schultz N, Thomas HD, et al: Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature 434: 913-917, 2005

22. Palma JP, Wang Y-C, Rodriguez LE, et al: ABT-888 confers broad in vivo activity in combination with temozolomide in diverse tumors. Clin Cancer Res 15: 7277-7290, 2009

23. Donawho CK, Luo Y, Luo Y, et al: ABT-888, an orally active poly(ADP-ribose) polymerase inhibitor that potentiates DNA-damaging agents in preclinical tumor models. Clin Cancer Res 13:2728-2737, 2007

24. Kumar-Sinha C, Tomlins SA, Chinnaiyan AM: Recurrent gene fusions in prostate cancer. Nat Rev Cancer 8:497-511, 2008

25. Tomlins SA, Rhodes DR, Perner S, et al: Recurrent fusion of TMPRSS2 and ETS transcription factor genes in prostate cancer. Science 310: 644-648, 2005

26. Brenner JC, Ateeq B, Li Y, et al: Mechanistic rationale for inhibition of poly(ADP-ribose) polymerase in ETS gene fusion-positive prostate cancer. Cancer Cell 19:664-678, 2011 [Erratum: Cancer Cell 23:557, 2013]

27. Kunju LP, Carskadon S, Siddiqui J, et al: Novel RNA hybridization method for the in situ detection of ETV1, ETV4, and ETV5 gene fusions in prostate cancer. Appl Immunohistochem Mol Morphol 22: e32-e40, 2014

28. Tomlins SA, Palanisamy N, Siddiqui J, et al: Antibody-based detection of ERG rearrangements in prostate core biopsies, including diagnostically challenging cases: ERG staining in prostate core biopsies. Arch Pathol Lab Med 136:935-946, 2012

29. Robinson D, Van Allen EM, Wu YM, et al: Integrative clinical genomics of advanced prostate cancer. Cell 161:1215-1228, 2015 [Erratum: Cell 162: 454, 2015]

30. McDaniel AS, Hovelson DH, Cani AK, et al: Genomic profiling of penile squamous cell carcinoma reveals new opportunities for targeted therapy. Cancer Res 75:5219-5227, 2015

31. Freidlin B, McShane LM, Korn EL: Randomized clinical trials with biomarkers: Design issues. J Natl Cancer Inst 102:152-160, 2010

32. Mateo J, Carreira S, Sandhu S, et al: DNA-repair defects and olaparib in metastatic prostate cancer. N Engl J Med 373:1697-1708, 2015

33. Park JJ, Irvine RA, Buchanan G, et al: Breast cancer susceptibility gene 1 (BRCAI) is a coactivator of the androgen receptor. Cancer Res 60:5946-5949, 2000

34. Shin S, Verma IM: BRCA2 cooperates with histone acetyltransferases in androgen receptor-mediated transcription. Proc Natl Acad Sci USA 100:7201-7206, 2003

35. Jiao J, Wang S, Qiao R, et al: Murine cell lines derived from Pten null prostate cancer show the critical role of PTEN in hormone refractory prostate cancer development. Cancer Res 67:6083-6091, 2007

36. Carver BS, Chapinski C, Wongvipat J, et al: Reciprocal feedback regulation of PI3K and androgen receptor signaling in PTEN-deficient prostate cancer. Cancer Cell 19:575-586, 2011

37. Ferraldeschi R, Nava Rodrigues D, Riisnaes R, et al: PTEN protein loss and clinical outcome from castration-resistant prostate cancer treated with abiraterone acetate. Eur Urol 67:795-802, 2015

38. Annala M, Struss WJ, Warner EW, et al: Treatment outcomes and tumor loss of heterozygosity in germline DNA repair-deficient prostate cancer. Eur Urol 72:34-42, 2017

Affiliations

Maha Hussain, Robert H. Lurie Comprehensive Cancer Center, Northwestern University; **Walter M. Stadler**, University of Chicago, Chicago; **Daniel H. Shevrin**, NorthShore University Health System, Evanston, IL; **Maha Hussain**, **Stephanie Daignault-Newton**, **Lakshmi P. Kunju**, **Javed Siddiqui**, **Yi-Mi Wu**, **Dan Robinson**, **Robert J. Lonigro**, **Xuhong Cao**, **Scott A. Tomlins**, **Rohit Mehra**, **David C. Smith**, **Megan V. Caram**, and **Arul M. Chinnaiyan**, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; **Przemyslaw W. Twardowski**, City of Hope Cancer Center, Duarte; **Felix Y. Feng**, University of California San Francisco, San Francisco, CA; **Costantine Albany**, Simon Cancer Center, Indiana University, Indianapolis, IN; **Mark N. Stein**, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; **Kathleen A. Cooney**, University of Utah, Salt Lake City, UT; **Bruce Montgomery**, University of Washington, Seattle, WA; **Emmanuel S. Antonarakis**, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; **Paul G. Corn**, University of Texas MD Anderson Cancer Center, Houston, TX; **Young E. Whang**, Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC; and **Karen E. Knudsen**, Thomas Jefferson University, Philadelphia, PA.

Support

Supported by Grants No. N01-CM-2011-00071C from the National Cancer Institute (NCI), SU2C-AACR-DT0712 from Stand up to Cancer and American Association for Cancer Research, P50CA186786 from NCI, PC080189 from the US Department of Defense, and the Prostate Cancer Foundation.

Prior Presentation

Presented at the 52nd Annual Meeting of the American Society of Clinical Oncology (ASCO), Chicago, IL, June 3-7, 2016, and 53rd ASCO Annual Meeting, Chicago, IL, June 2-6, 2017.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Targeting Androgen Receptor and DNA Repair in Metastatic Castration-Resistant Prostate Cancer: Results From NCI 9012

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

Maha Hussain
Honoraria: Sanofi, Onclive
Research Funding: Genentech (Inst), Pfizer (Inst), Prostate Cancer Clinical Trials Consortium (Inst), Bayer HealthCare Pharmaceuticals (Inst), AstraZeneca (Inst)
Patents, Royalties, Other Intellectual Property: Systems and methods for tissue imaging, 3676 Our File: Serial No.: UM-14437/US-1/PRO 60/923,385 UM-14437/US-2/ORD 12/101,753US 8,185,186 (US patent No.), Systems and methods for tissue imaging (issued patent) EP 08745653.9 (EP application No.), Systems and methods for tissue imaging (pending) CA 2683805 (Canadian application No.), Systems and methods for tissue imaging (pending) US 13/362,500 (US application No.), Systems and methods for tissue imaging (continuation application of US 8,185,186); Method of treating cancer docket No: serial No.: 224990/10-016P2/311733 61/481/671, application filed on February 5, 2011; Dual inhibition of MET and VEGF for the treatment of castration resistant prostate cancer and osteoblastic bone metastases, applicant/proprietor Exelexis, application No./patent No. 11764665.4- 1464, application No./patent No. 11764656.2-1464, application filed on September 26, 2011
Travel, Accommodations, Expenses: Sanofi

Stephanie Daignault-Newton
Consulting or Advisory Role: Augmenix
Research Funding: Pfizer (Inst), Bayer HealthCare Pharmaceuticals (Inst)

Przemyslaw W. Twardowski
No relationship to disclose

Costantine Albany
Stock or Other Ownership: Advaxis
Honoraria: Sanofi
Consulting or Advisory Role: Seattle Genetics, AstraZeneca/MedImmune
Speakers' Bureau: Bayer HealthCare Pharmaceuticals, Sanofi
Research Funding: Astex Pharmaceuticals (Inst), Seattle Genetics (Inst), Tesaro (Inst), Bristol-Myers Squibb (Inst)

Mark N. Stein
Research Funding: Oncoceutics (Inst), Merck Sharp & Dohme (Inst), AbbVie (Inst), Janssen Oncology (Inst), Medivation (Inst), Astellas Pharma (Inst), Advaxis (Inst), Bavarian Nordic (Inst), Suzhou Kintor Pharmaceuticals (Inst)

Lakshmi P. Kunju
No relationship to disclose

Javed Siddiqui
No relationship to disclose

Yi-Mi Wu
No relationship to disclose

Dan Robinson
No relationship to disclose

Robert J. Lonigro
No relationship to disclose

Xuhong Cao
Consulting or Advisory Role: Tempus
Patents, Royalties, Other Intellectual Property: Tempus

Scott A. Tomlins
Leadership: Strata Oncology
Consulting or Advisory Role: Ventana Medical Systems, AbbVie, Janssen Pharmaceuticals, Astellas Pharma, Medivation, Roche, Strata Oncology, Sanofi, Almac Diagnostics
Research Funding: Thermo Fisher Scientific (Inst), Compendia Bioscience (Inst), Life Technologies (Inst), Astellas Pharma (Inst), Medivation (Inst), GenomeDx (Inst)
Patents, Royalties, Other Intellectual Property: coauthor on patent issued to the University of Michigan on ETS gene fusions inprostate cancer; diagnostic field of use has been licensed to Hologic/Gen-Probe, which has sublicensed some rights to Ventana Medical Systems/Roche
Travel, Accommodations, Expenses: Thermo Fisher Scientific, Strata Oncology

Rohit Mehra
Patents, Royalties, Other Intellectual Property: Holgic

Kathleen A. Cooney
Patents, Royalties, Other Intellectual Property: patent on discovery of HOXB13 as prostate cancer susceptibility gene (Inst)

Bruce Montgomery
Research Funding: ESSA, Medivation, Janssen Oncology, Astellas Pharma, Clovis Oncology

Emmanuel S. Antonarakis
Honoraria: Sanofi, Dendreon, Medivation, Janssen Biotech, ESSA, Astellas Pharma
Consulting or Advisory Role: Sanofi, Dendreon, Medivation, Janssen Biotech, ESSA, Astellas Pharma
Research Funding: Janssen Biotech (Inst), Johnson & Johnson (Inst), Sanofi (Inst), Dendreon (Inst), Aragon Pharmaceuticals (Inst), Exelixis (Inst), Millennium Pharmaceuticals (Inst), Genentech (Inst), Novartis (Inst), Astellas Pharma (Inst), Tokai Pharmaceuticals (Inst)
Travel, Accommodations, Expenses: Sanofi, Dendreon, Medivation

Daniel H. Shevrin
Honoraria: Sanofi
Speakers' Bureau: Bayer HealthCare Pharmaceuticals

Paul G. Corn
No relationship to disclose

Young E. Whang
Research Funding: Astellas Pharma, Medivation, Inovio Pharmaceuticals, Tokai Pharmaceuticals, Innocrin Pharma

David C. Smith
Research Funding: Agensys (Inst), Atterocor (Inst), Millendo Therapeutics (Inst), Bayer HealthCare Pharmaceuticals (Inst), Boston Biomedical (Inst), Celgene (Inst), Exelixis (Inst), ImClone Systems (Inst), Incyte (Inst), Eli Lilly (Inst), MedImmune (Inst), Millennium Pharmaceuticals (Inst), Novartis (Inst), Oncogenex (Inst), OncoMed (Inst), Seattle Genetics (Inst), TEVA Pharmaceuticals Industries (Inst), Tekmira (Inst), Bristol-Myers Squibb (Inst), Medarex (Inst), ESSA (Inst), Genentech (Inst), Medivation (Inst), Astellas Pharma (Inst), Takeda Pharmaceuticals (Inst)

Megan V. Caram
No relationship to disclose

Karen E. Knudsen
Stock or Other Ownership: Novartis, Pfizer
Honoraria: Celgene, CellCentric, Sanofi, Janssen Pharmaceuticals
Consulting or Advisory Role: CellCentric
Research Funding: Celgene

Walter M. Stadler
Honoraria: CVS Caremark, Sotio, AstraZeneca, Bristol-Myers Squibb, Roche, Genentech
Consulting or Advisory Role: CVS Caremark, Sotio, AstraZeneca, Bristol-Myers Squibb
Research Funding: Active Biotech (Inst), Bayer HealthCare Pharmaceuticals (Inst), Bristol-Myers Squibb (Inst), Boehringer Ingelheim (Inst), Dendreon (Inst), Exelixis (Inst), Novartis (Inst), Genentech (Inst), Roche (Inst), GlaxoSmithKline (Inst), Medivation (Inst), Pfizer (Inst), Merck (Inst), Millennium Pharmaceuticals (Inst), Janssen Pharmaceuticals (Inst), Johnson & Johnson (Inst)
Other relationship: UpToDate, American Cancer Society

Felix Y. Feng
Leadership: PFS Genomics
Stock or Other Ownership: PFS Genomics
Consulting or Advisory Role: Medivation, Astellas Pharma, GenomeDx, Celgene, Dendreon, EMD Serono, Janssen Oncology, Ferring, Bayer HealthCare Pharmaceuticals, Clovis Oncology
Research Funding: Varian Medical Systems, Celgene
Patents, Royalties, Other Intellectual Property: Helped develop a molecular signature to predict radiation resistance in breast cancer, and this signature was patented by the University of Michigan, my employer; it is in the process of being licensed to PFS Genomics, a company that I helped found (Inst)

Arul M. Chinnaiyan
No relationship to disclose

Acknowledgment

We thank Stephanie Ellison for assistance in formatting and writing this manuscript as well as the Mi-Oncoseq clinical sequencing laboratory for sequence analysis of samples in this study. We are especially grateful to all the patients who participated in this investigational study. We would also like to thank the Michigan Center for Translational Pathology.

Appendix

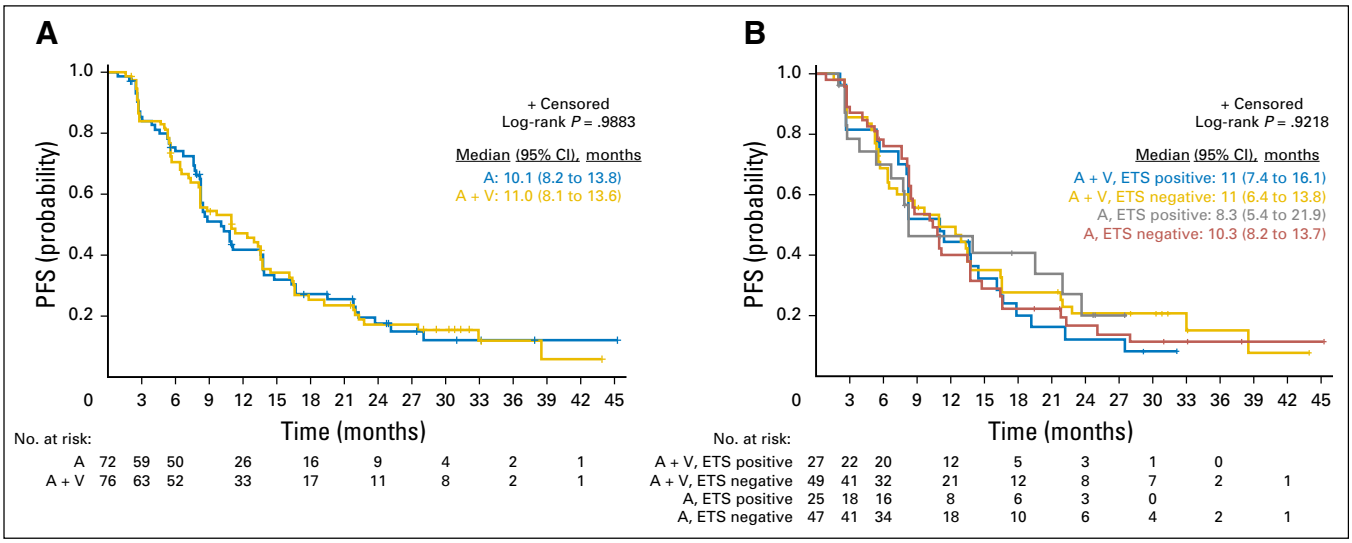


Fig A1. Progression-free survival (PFS) in patients with metastatic castration-resistant prostate cancer treated with abiraterone (A) or abiraterone plus veliparib (A + V) and stratified by ETS gene fusion status. (A) PFS curves are shown for all 148 response-evaluable patients treated with abiraterone/prednisone alone (n = 72) or in combination with veliparib (n = 76). (B) PFS curves are shown for each treatment arm stratified by ETS gene fusion status (determined by immunohistochemistry or in situ hybridization).

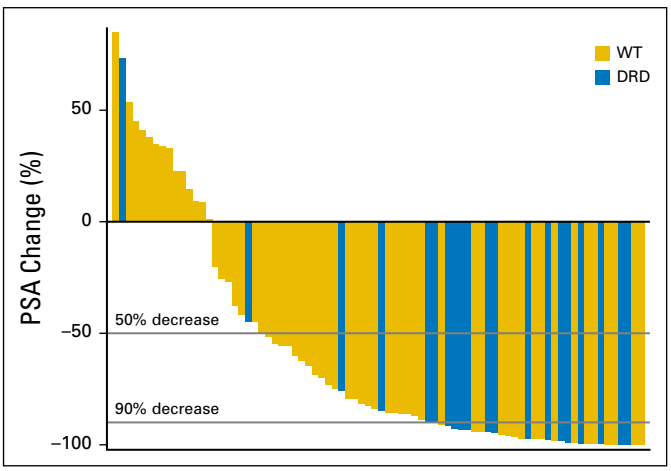


Fig A2. Depth of prostate-specific antigen (PSA) decline by DNA-damage repair defect (DRD) status. WT, wild type.

Table A1. Demographic and Clinical Characteristics of Patients by Tumor Sequencing Status

Characteristic	No. (%) Sequenced (n = 80)	No. (%) Not Sequenced (n = 68)	*P*
Age, years			.44
Median	68	68	
Range	50-85	55-90	
Race			.67
White	69 (86.3)	62 (91.2)	
Black	7 (8.8)	4 (5.9)	
Other	4 (5.0)	2 (2.9)	
Performance status			.88
0	50 (62.5)	43 (63.2)	
1	29 (36.3)	25 (36.8)	
2	1 (1.3)	0	
PSA, ng/mL			.59
Median	36.8	31.0	
Range	0.04-1,557.6	0.5-940.7	
Cancer pain present	28 (35.0)	18 (26.5)	.26
Sites of disease			
Bone	66 (82.5)	62 (91.2)	.12
Lymph node	62 (77.5)	33 (48.5)	< .001
Visceral	20 (25.0)	14 (20.6)	.52
Other	15 (18.8)	13 (19.1)	.95
Previous treatment			
Chemotherapy	25 (31.3)	13 (19.1)	.09
Docetaxel/cabazitaxel	17 (21.3)	10 (14.7)	
Other	8 (10.0)	3 (4.4)	
Enzalutamide	2 (2.5)	2 (2.9)	.99
Sipuleucel-T	19 (23.8)	15 (22.1)	.85
Experimental agent	18 (22.5)	16 (23.5)	.88
Strata: ETS fusion and ketoconazole use			< .001
ETS fusion positive*	39 (48.8)	13 (19.1)	
ETS fusion negative	41 (51.3)	55 (80.9)	
Previous ketoconazole	10 (12.5)	6 (8.8)	.60
Treatment arm			.05
Abiraterone	33 (41.3)	39 (57.4)	
Abiraterone + veliparib	47 (58.8)	29 (42.7)	
No. of treatment cycles			.79
Median	9	9	
Range	2-50	1-46	
PSA response rate, %	65.0	72.1	.36
Measurable disease	60 (75.0)	26 (38.2)	< .001
Objective response, %	51.7	42.3	.43
PFS, months			.47
Median	10.3	10.8	
95% CI	8.0 to 13.8	8.2 to 13.7	
OS, months			.90
Median	32.3	30.6	
95% CI	24.1 to NR	28.1 to NR	

Abbreviations: NR, not reached; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen.
*ETS fusion determined by immunohistochemistry/in situ hybridization.

Table A2. Baseline Covariates Among Patients With Tumor Sequencing

Characteristic	No. (%) Abiraterone (n = 33)	No. (%) Abiraterone + Veliparib (n = 47)	*P*
Age, years			.22
Median	70	68	
Range	50-80	52-86	
Race			.61
White	27 (81.8)	42 (89.4)	
Black	4 (12.1)	3 (6.4)	
Other	2 (6.1)	2 (4.3)	
Performance status			.50
0	19 (57.6)	31 (66.0)	
1	14 (42.4)	15 (31.9)	
2	0	1 (2.1)	
PSA, ng/mL			.87
Median	35.2	39.2	
Range	2-1,557.6	0.04-785.8	
Cancer pain present	14 (42.4)	14 (29.8)	.24
Sites of disease			
Bone	15 (45.5)	27 (57.5)	.29
Lymph node	24 (72.7)	38 (80.9)	.39
Visceral	6 (18.2)	14 (29.8)	.18
Other	6 (18.2)	9 (19.2)	.91
Previous treatments			
Chemotherapy	9 (27.3)	16 (34.0)	.52
Docetaxel/cabazitaxel	5 (15.2)	12 (25.5)	
Other	4 (12.1)	4 (8.5)	
Enzalutamide	1 (3.0)	1 (2.1)	.99
Sipuleucel-T	12 (36.4)	7 (14.9)	.03
Experimental agent	8 (24.2)	10 (21.3)	.75
Strata: ETS fusion and ketoconazole use			.68
ETS fusion positive	17 (51.5)	22 (46.8)	
ETS fusion negative	16 (48.5)	25 (53.2)	
Previous ketoconazole	5 (15.2)	5 (10.6)	.73
No. of treatment cycles			.58
Median	9	9	
Range	2-39	2-50	
Confirmed PSA response	18 (54.6)	34 (72.3)	.10
Measurable disease response	11 (45.8)	20 (55.6)	.46
PFS, months			.89
Median	8.8	11.0	
95% CI	6.7 to 13.8	7.4 to 13.8	
OS, months			—
Median	29.4	32.3	
95% CI	17.4 to NR	24.1 to NR	

Abbreviations: NR, not reached; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen.

Table A3. AEs by Treatment Arm

AE	No. (%)											
	Arm A: Abiraterone (n = 74)						Arm B: Abiraterone + Veliparib (n = 79)					
	Grade						Grade					
	1	2	3	4	5	Total	1	2	3	4	5	Total
ALT increased	8 (11)	1 (1)	3 (4)	0 (0)	0 (0)	12 (16)	4 (5)	0 (0)	2 (3)	0 (0)	0 (0)	6 (8)
Alkaline phosphatase increased	3 (4)	2 (3)	0 (0)	0 (0)	0 (0)	5 (7)	2 (3)	4 (5)	2 (3)	0 (0)	0 (0)	8 (10)
Anemia	9 (12)	1 (1)	1 (1)	0 (0)	0 (0)	11 (15)	10 (13)	4 (5)	2 (3)	0 (0)	0 (0)	16 (20)
Anorexia	3 (4)	0 (0)	0 (0)	0 (0)	0 (0)	3 (4)	5 (6)	5 (6)	0 (0)	0 (0)	0 (0)	10 (13)
Arthralgia	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	2 (3)
AST increased	14 (19)	2 (3)	0 (0)	0 (0)	0 (0)	16 (22)	6 (8)	2 (3)	0 (0)	0 (0)	0 (0)	8 (10)
Atrial fibrillation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
Cardiac arrest	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)
Confusion	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
Dehydration	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (3)	1 (1)	0 (0)	0 (0)	3 (4)
Diarrhea	4 (5)	1 (1)	0 (0)	0 (0)	0 (0)	5 (7)	10 (13)	2 (3)	0 (0)	0 (0)	0 (0)	12 (15)
Dizziness	2 (3)	0 (0)	0 (0)	0 (0)	0 (0)	2 (3)	7 (9)	1 (1)	0 (0)	0 (0)	0 (0)	8 (10)
Edema limbs	13 (18)	2 (3)	0 (0)	0 (0)	0 (0)	15 (20)	5 (6)	0 (0)	0 (0)	0 (0)	0 (0)	5 (6)
Ejection fraction decreased	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
Fatigue	18 (24)	2 (3)	0 (0)	0 (0)	0 (0)	20 (27)	31 (39)	8 (10)	0 (0)	0 (0)	0 (0)	39 (49)
Glucose intolerance	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Headache	6 (8)	0 (0)	0 (0)	0 (0)	0 (0)	6 (8)	5 (6)	1 (1)	1 (1)	0 (0)	0 (0)	7 (9)
Heart failure	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hot flashes	8 (11)	1 (1)	0 (0)	0 (0)	0 (0)	9 (12)	16 (20)	0 (0)	0 (0)	0 (0)	0 (0)	16 (20)
Hyperglycemia	3 (4)	1 (1)	6 (8)	1 (1)	0 (0)	11 (15)	6 (8)	2 (3)	4 (5)	0 (0)	0 (0)	12 (15)
Hypertension	2 (3)	6 (8)	3 (4)	0 (0)	0 (0)	11 (15)	3 (4)	2 (3)	3 (4)	0 (0)	0 (0)	8 (10)
Hypokalemia	6 (8)	0 (0)	0 (0)	0 (0)	0 (0)	6 (8)	7 (9)	1 (1)	1 (1)	0 (0)	0 (0)	9 (11)
Hypophosphatemia	3 (4)	4 (5)	1 (1)	0 (0)	0 (0)	8 (11)	2 (3)	4 (5)	1 (1)	0 (0)	0 (0)	7 (9)
Hypotension	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
Insomnia	4 (5)	0 (0)	0 (0)	0 (0)	0 (0)	4 (5)	8 (10)	2 (3)	1 (1)	0 (0)	0 (0)	11 (14)
Lymphocyte count decreased	3 (4)	1 (1)	1 (1)	0 (0)	0 (0)	5 (7)	6 (8)	8 (10)	1 (1)	0 (0)	0 (0)	15 (19)
Nausea	5 (7)	0 (0)	0 (0)	0 (0)	0 (0)	5 (7)	29 (37)	12 (15)	1 (1)	0 (0)	0 (0)	42 (53)
Pain	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	2 (3)	1 (1)	1 (1)	0 (0)	0 (0)	4 (5)
Platelet count decreased	2 (3)	1 (1)	0 (0)	0 (0)	0 (0)	3 (4)	5 (6)	1 (1)	1 (1)	1 (1)	0 (0)	8 (10)
Respiratory, thoracic, and mediastinal disorders–other	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
Sinus tachycardia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
Syncope	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
Thromboembolic event	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (3)	0 (0)	0 (0)	2 (3)
Vomiting	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	12 (15)	5 (6)	0 (0)	0 (0)	0 (0)	17 (22)
Maximum grade for patient	27 (36)	15 (20)	15 (20)	1 (1)	0 (0)	58 (78)	24 (30)	28 (35)	19 (24)	1 (1)	1 (1)	73 (92)

Abbreviation: AE, adverse event.

Table A4. ETS Gene Fusion Agreement Between Trial Methods and Sequencing

ETS Status by Trial Methods*	ETS Status by Sequencing No. (%)	
	Negative	Positive
Negative	36 (45.0)	5 (6.25)
Positive	3 (3.75)	36 (45.0)
Agreement	72 (90) of 80	

*Trial methods: immunohistochemistry and in situ hybridization/fluorescence in situ hybridization.

Table A5. Biomarker Prognostic Analysis: Overall PSA Response, Measurable Disease Response, and PFS by Biomarker Status

Response/PFS	Biomarker Status		*P*
	Not Normal	Normal	
Confirmed PSA response	No. (%)		
ETS (positive [n = 41] *v* negative [n = 39])	25 (61.0)	27 (69.2)	.44
DNA repair (defect [n = 20] *v* WT/monoallelic [n = 60])	18 (90.0)	34 (56.7)	.007
AR (amplified/mutated [n = 41] *v* normal [n =39])	25 (61.0)	27 (69.2)	.44
TP53 (mutated [n = 33] *v* normal [n = 47])	20 (60.6)	32 (68.1)	.49
PTEN (mutated [n = 34] *v* normal [n = 46])	17 (50.0)	35 (76.1)	.016
PIK3CA pathway (activated [n = 39] *v* normal [n = 41])	22 (56.4)	30 (73.2)	.12
WNT pathway (activated [n = 12] *v* normal [n = 68])	8 (66.7)	44 (64.7)	.99
RB1 (mutated [n = 9] *v* normal [n = 71])	6 (66.7)	46 (64.8)	.99
CHD1 (mutated [n = 4] *v* normal [n = 76])	3 (75.0)	49 (64.5)	.99
SPOP (mutated [n = 5] *v* normal [n = 75])	4 (80.0)	48 (64.0)	.65
ZFHX3 (mutated [n = 6] *v* normal [n = 74])	3 (50.0)	49 (66.2)	.42
Measurable disease response			
ETS (positive [n = 31] *v* negative [n = 29])	15 (48.4)	16 (55.2)	.60
DNA repair (defect [n = 16] *v* WT/monoallelic [n = 44])	14 (87.5)	17 (38.6)	.001
AR (amplified/mutated [n = 29] *v*normal [n = 31])	13 (44.8)	18 (58.1)	.31
TP53 (mutated [n = 24] *v* normal [n = 36])	10 (41.7)	21 (58.3)	.21
PTEN (mutated [n = 28] *v* normal [n = 32])	12 (42.9)	19 (59.4)	.20
PIK3CA pathway (activated [n = 29] *v* normal [n = 31])	13 (44.8)	18 (58.1)	.31
WNT pathway (activated [n = 8] *v* normal [n = 52])	3 (37.5)	28 (53.9)	.47
RB1 (mutated [n = 4] *v* normal [n = 56])	2 (50.0)	29 (51.8)	.99
CHD1 (mutated [n = 3] *v* normal [n = 57])	2 (66.7)	29 (50.9)	.99
SPOP (mutated [n = 4] *v* normal [n = 56])	3 (75.0)	28 (50.0)	.61
ZFHX3 (mutated [n = 5] *v* normal [n = 55])	3 (60.0)	28 (50.9)	.99
PFS, months	Median (95% CI)		
ETS (positive [n = 41] *v* negative [n = 39])	8.2 (5.4 to 14.5)	13.3 (8.2 to 13.8)	.48
DNA repair (defect [n = 20] v WT/monoallelic [n = 60])	14.5 (11.0 to 19.5)	8.1 (5.5 to 11.0)	.025
AR (amplified/mutated [n = 41] *v* normal [n = 39])	8.8 (5.4 to 13.5)	11.0 (8.0 to 16.6)	.17
TP53 (mutated [n = 33] *v* normal [n = 47])	7.7 (5.3 to 8.8)	13.5 (8.2 to 16.6)	.01
PTEN (mutated [n = 34] *v* normal [n = 46])	6.7 (4.1 to 11.3)	13.5 (8.2 to 16.6)	.02
PIK3CA pathway (activated [n = 39] *v* normal [n = 41])	8.3 (5.4 to 13.3)	13.8 (8.2 to 16.6)	.03
WNT pathway (activated [n = 12] *v* normal [n = 68])	12.4 (2.7 to 23.7)	10.3 (8.0 to 13.6)	.91
RB1 (mutated [n = 9] *v* normal [n = 71])	8.8 (1.9 to 23.7)	10.3 (8.0 to 13.8)	.46
CHD1 (mutated [n = 4] *v* normal [n = 76])	NR (2.6 to NR)	8.8 (7.8 to 13.6)	.09
SPOP (mutated [n = 5] *v* normal [n = 75])	NR (2.8 to NR)	8.8 (7.8 to 13.6)	.06
ZFHX3 (mutated [n = 6] *v* normal [n = 74])	10.0 (2.1 to 13.8)	10.3 (8.0 to 13.8)	.20

Abbreviations: NR, not reached; PFS, progression-free survival; PSA, prostate-specific antigen.

Table A6. Biomarker Predictive Analysis: Overall PSA Response, Measurable Disease Response, and PFS by Biomarker Status and Treatment Arm

Response/PFS	Marker Not Normal			Marker Normal			Interaction *P*
	Abiraterone	Abiraterone + Veliparib	*P*	Abiraterone	Abiraterone + Veliparib	*P*	
Confirmed PSA response	No. (%)			No. (%)			
ETS (positive [n = 41] *v* negative [n = 39])	8 (44.4)	17 (73.9)	.05	10 (66.7)	17 (70.8)	.78	.27
DNA repair (defect [n = 20] *v* WT/monoallelic [n = 60])	6 (85.7)	12 (92.3)	1.0	12 (46.2)	22 (64.7)	.15	.97
AR (amplified/mutated [n = 41] *v* normal [n = 39])	9 (47.4)	16 (72.7)	.097	9 (64.3)	18 (72.0)	.72	.45
PTEN (mutated [n = 34] *v* normal [n = 46])	5 (35.7)	12 (60.0)	.16	13 (68.4)	22 (81.5)	.31	.78
TP53 (mutated [n = 33] *v* normal [n = 47])	9 (60.0)	11 (61.1)	.95	9 (50.0)	23 (79.3)	.036	.18
PIK3CA pathway (activated [n = 39] *v* normal [n = 41])	6 (40.0)	16 (66.7)	.10	12 (66.7)	18 (78.3)	.41	.60
WNT pathway (activated [n = 12] *v* normal [n = 68])	3 (42.9)	5 (100.0)	.08	15 (57.7)	29 (69.1)	.34	.95
Measurable disease response	No. (%)			No. (%)			
ETS (positive [n = 31] *v* negative [n = 29])	6 (42.9)	9 (52.9)	.58	5 (50.0)	11 (57.9)	.68	.94
DNA repair (defect [n = 16] *v* WT/monoallelic [n = 44])	4 (80.0)	10 (90.9)	1.00	7 (36.8)	10 (40.0)	.83	.64
AR (amplified/mutated [n = 29] *v* normal [n = 31])	4 (36.4)	9 (50.0)	.70	7 (53.9)	11 (61.1)	.69	.81
PTEN (mutated [n = 28] *v* normal [n = 32])	5 (45.5)	7 (41.2)	.82	6 (46.2)	13 (68.4)	.21	.31
TP53 (mutated [n = 24] *v* normal [n = 36])	5 (50.0)	5 (35.7)	.68	6 (42.9)	15 (68.2)	.18	.14
PIK3CA pathway (activated [n = 29] *v* normal [n = 31])	5 (45.5)	8 (44.4)	.96	6 (46.2)	12 (66.7)	.25	.41
WNT pathway (activated [n = 8] *v* normal [n = 52])	0 (0.0)	3 (75.0)	.14	11 (55.0)	17 (53.1)	.90	.97
PFS, months	Median (95% CI)			Median (95% CI)			
ETS (positive [n = 41] *v* negative [n = 39])	7.7 (2.7 to 19.5)	11.0 (7.4 to 17.9)	.29	13.8 (8.2 to 16.6)	11.0 (5.5 to 13.8)	.33	.20
DNA repair (defect [n = 20] *v* WT/monoallelic [n = 60])	16.6 (13.5 to 19.5)	13.8 (8.2 to 32.9)	.93	8.2 (3.9 to 10.3)	8.1 (5.3 to 13.6)	.79	.89
AR (amplified/mutated [n = 41] *v* normal [n = 39])	8.3 (2.8 to 16.6)	8.8 (5.4 to 13.8)	.87	10.3 (6.7 to NR)	11.0 (6.4 to 17.9)	.60	.52
PTEN (mutated [n = 34] *v* normal [n = 46])	6.7 (2.6 to 19.5)	6.9 (2.8 to 13.6)	.55	13.5 (7.8 to 16.6)	13.8 (8.1 to 19.2)	.69	.40
TP53 (mutated [n = 33] *v* normal [n = 47])	8.3 (3.9 to 13.8)	5.7 (2.8 to 8.8)	.30	13.5 (2.7 to 16.6)	13.8 (8.2 to 17.9)	.84	.31
PIK3CA pathway (activated [n = 39] *v* normal [n = 41])	8.3 (2.6 to 19.5)	11.0 (5.3 to 13.6)	.62	13.8 (7.7 to 16.6)	13.8 (7.4 to 22.2)	.77	.51
WNT pathway (activated [n = 12] *v* normal [n = 68])	8.3 (1.9 to 23.7)	16.5 (5.4 to 32.9)	.74	8.8 (5.4 to 13.8)	11.0 (7.4 to 13.8)	.85	.80

NOTE. Markers included but too small of a mutation/aberrant representative sample size by treatment arm for analysis: *RB1*, *CHD1*, *SPOP*, and *ZFHX3*.
Abbreviations: NR, not reached; PFS, progression-free survival; PSA, prostate-specific antigen.

Table A7. Multivariable Analysis of PFS

Covariate	Hazard Ratio (95% CI)		
	Unadjusted Univariable Analysis		Multivariable Cox Model
	All Patients	Sequenced Patients Only	Sequenced Patients Only
Clinical			
Treatment arm			
Abiraterone + veliparib *v* abiraterone	1.00 (0.70 to 1.44)	1.04 (0.62 to 1.72)	1.00 (0.58 to 1.72)
ETS fusion status			
Positive *v* negative	1.06 (0.72 to 1.56)	1.19 (0.73 to 1.95)	1.05 (0.60 to 1.83)
Prior ketoconazole	1.96 (1.11 to 3.46)	1.62 (0.79 to 3.31)	1.57 (0.74 to 3.36)
Age	1.02 (1.00 to 1.05)	1.04 (1.002 to 1.07)	1.04 (1.00 to 1.08)
Race			
Black *v* white	0.87 (0.44 to 1.73)	0.58 (0.23 to 1.44)	0.49 (0.18 to 1.34)
Other *v* white	0.65 (0.24 to 1.78)	0.35 (0.09 to 1.44)	0.29 (0.07 to 1.31)
Performance status			
Symptomatic *v* normal	2.00 (1.37 to 2.92)	2.27 (1.35 to 3.80)	2.02 (1.16 to 3.53)
Baseline PSA (log transformed)	1.13 (1.00 to 1.27)	1.09 (0.92 to 1.29)	1.02 (0.88 to 1.19)
Previous chemotherapy	2.09 (1.39 to 3.13)	2.19 (1.31 to 3.66)	2.00 (1.12 to 3.54)
Previous enzalutamide	5.48 (1.98 to 15.2)	Inf (2.0 to Inf)	—
Biomarkers*			
DNA repair (defect *v* WT/monoallelic)		0.52 (0.29 to 0.93)	0.51 (0.27 to 0.97)
AR (amplified/mutated *v* normal)		1.41 (0.86 to 2.31)	1.34 (0.80 to 2.23)
TP53 (mutated *v* normal)		1.88 (1.14 to 3.12)	2.52 (1.30 to 4.89)
PTEN (mutated *v* normal)		1.82 (1.11 to 3.01)	1.61 (0.92 to 2.82)
PIK3CA pathway (activated *v* normal)		1.74 (1.05 to 2.87)	1.45 (0.79 to 2.68)
WNT pathway (activated *v* normal)		0.96 (0.50 to 1.85)	0.88 (0.44 to 1.74)
RB1 (mutated *v* normal)		1.32 (0.62 to 2.78)	1.47 (0.66 to 3.28)
CHD1 (mutated *v* normal)		0.31 (0.07 to 1.29)	0.39 (0.09 to 1.71)
SPOP (mutated *v* normal)		0.28 (0.07 to 1.15)	0.54 (0.09 to 3.40)
ZFHX3 (mutated *v* normal)		1.74 (0.74 to 4.09)	1.44 (0.57 to 3.63)
ETS fusion by sequencing (positive *v* negative)		1.19 (0.73 to 1.95)	1.24 (0.45 to 3.38)

Abbreviations: PFS, progression-free survival; PSA, prostate-specific antigen.
*Biomarkers were added separately and individually to the multivariable model containing clinical covariates.

Table A8. Exceptional Responder Data

						DRD		Mutated			Activated		Mutated		Prior Treatments			PFS		PSA (ng/mL)					Metastatic Biopsy Site	Disease Site	Bone Disease			
Patient ID	Site	Age (years)	Race	Treatment Group	ETS Fusions	DRD	Genes	*AR*	*PTEN*	*TP53*	PI3K	WNT	*SPOP*	*CHD1*	Chemotherapy	Other	Ketoconazole	Months	Progression (1) or Censored (0)	Baseline	Nadir	Maximum Change (%)	Confirmed Response	Confirmed CR			No. of Lesions at Baseline	Maximum Change in Measurable Disease (%)	Type of Lesion	RECIST Comments
Sequenced																													
43	UM	72	White	A + V	–	DRD BA	*BRCA2*	Y	N	N	N	N	N	Y	None	N	N	44	0	112.9	0.1	−100	Y	Y	Liver	Bone and visceral	2-4	−80	2 hepatic masses and 2 iliac LNs	1 hepatic mass had 80% reduction in size, and other hepatic mass decreased in size by 76%; 1 LN returned to normal; 1 LN decreased by two thirds
53	COH	66	White	A + V	–	DRD BA	*BRCA2*	N	N	N	N	N	N	N	None	N	N	39	1	16.39	0.04	−100	Y	Y	LN	Bone and visceral	2-4	−81	5 LNs	2 retroperitoneal LNs returned to normal; nontarget pulmonary nodule remained stable; progression by new liver metastases
85	UM	53	Black	A + V	+	DRD BA	*RAD51B, RAD51C*	N	N	N	N	Y	N	N	Other	N	N	33	1	55.2	3.9	−93	Y	N	LN	Bone ± LN	5-9	−57	1 LN	Lateral external iliac LN mass; progression in LN mass
119	MDA	58	White	A + V	+	DRD BA	*BRCA2*	N	N	N	N	N	N	N	Doc/cab	N	N	29	0	8.8	0.5	−94	Y	N	LN	Bone and visceral	5-9	−46	2 masses; 1 LN	2 masses reduced approximately 40% each; LN shrank by 56%
125	COH	60	White	A + V	–	DRD MA	*BRCA1*	N	N	N	N	N	N	N	None	Y	N	31	0	33.86	2.05	−94	Y	N	LN	Visceral or other	0	−90	1 mass	Pubic ramus–associated soft tissue
34	COH	80	Other	A	–	WT		N	N	N	N	N	Y	N	None	Y	N	33	0	25.68	0.0	−100	Y	Y	LN	Visceral or other	0	−100	Left upper lung nodule and 3 LNs	Lung nodule went from 11 at baseline to 0 at 3-month scan; LNs decreased from first scan through 19.5-month scan when CR was attained; CR was confirmed 3 months after initial CR (22.5 months on trial)
70	COH	72	White	A	+	WT		CG	Y	Y	Y	N	N	N	None	Y	N	25	0	39.74	0.13	−100	Y	Y	LN	LN only	0	−32	3 LNs	1 LN remained stable; 2 decreased; patient continued receiving A after departing trial after 1 year and remained stable in follow- up
82	COH	62	White	A+V	+	WT		Amp	Y	Y	Y	N	N	N	None	Y	N	27	1	1.92	0.0	−100	Y	Y	LN	Visceral or other	0	−58		1 nodule reduced by 40%; 1 LN reduced to normal; 1 LN decreased and remained stable
107	UNC	75	Black	A	–	WT		N	Y	N	Y	N	Y	N	None	N	N	31	0	35.2	0.1	−100	Y	Y	LN	Bone ± LN	1	−64	2 LNs	1 LN reduced from 33 to 11, and other LN reduced from 14 to 6
Not sequenced																														
40	CINJ	64	White	A	+	ND									None	N	N	27	0	20.87	0.42	−98	Y	N	Bone	Bone ± LN	2-4			
44	COH	70	White	A + V	–	ND									None	N	N	28	0	2.41	0	−100	Y	Y	Bone	Bone ± LN	> 20			
49	IU	74	White	A	–	ND									None	N	N	45	0	93.942	0.008	−100	Y	Y	Bone	Bone ± LN	> 20			
77	NS	65	White	A	–	ND									None	Y	N	38	0	6.36	0.02	−100	Y	Y	Bone	Bone ± LN	2-4			
102	COH	61	White	A + V	–	ND									None	Y	N	33	0	151.31	0	−100	Y	Y	Bone	Bone ± LN	5-9			
113	UWASH	67	White	A + V	–	ND									None	N	N	31	0	0.95	0.03	−97	Y	Y	Bone	Bone ± LN	5-9			
132	CINJ	62	White	A + V	+	ND									None	Y	N	32	0	159.5	1.46	−99	Y	N	Bone	Bone ± LN	5-9			
138	COH	74	White	A + V	–	ND									None	Y	N	30	0	1.22	0	−100	Y	Y	Bone	Bone ± LN	5-9			
146	UM	62	White	A	+	ND									None	N	N	25	0	11	0.1	−99	Y	Y	LN	LN only	0			
162	UM	60	White	A	–	ND									None	N	N	25	1	9.7	0.1	−99	Y	Y	Bone	Bone and visceral	10-20			

NOTE. Exceptional responders were patients with > 24 months PFS and > 90% PSA response.

Abbreviations: A, abiraterone; amp, amplified; BA, biallelic; cab, cabozantinib; CG, copy gain; CINJ, Cancer Institute of New Jersey; COH, City of Hope; CR, complete response; doc, docetaxel; DRD, DNA-damage repair defect; IU, Indiana University; LN, lymph node; MA, monoallelic; MDA, MD Anderson; ND, not determined; NS, NorthShore; PFS, progression-free survival; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors; UM, University of Michigan; UNC, University of North Carolina; UWASH, University of Washington; V, veliparib; WT, wild type.

Prostate Cancer and Prostatic Diseases (2018) 21:364–372
https://doi.org/10.1038/s41391-017-0009-6

ARTICLE

Post prostatectomy outcomes of patients with high-risk prostate cancer treated with neoadjuvant androgen blockade

Rana R. McKay[1] · Bruce Montgomery[2] · Wanling Xie[3] · Zhenwei Zhang[4] · Glenn J. Bubley[5] · David W. Lin[6] · Mark A. Preston[7] · Quoc-Dien Trinh[7] · Peter Chang[8] · Andrew A. Wagner[8] · Elahe A. Mostaghel[2] · Philip W. Kantoff[9] · Peter S. Nelson[2] · Adam S. Kibel[7] · Mary-Ellen Taplin[4]

Received: 9 June 2017 / Revised: 14 August 2017 / Accepted: 6 September 2017 / Published online: 20 December 2017

Abstract

Background Patients with high-risk prostate cancer have an increased likelihood of experiencing a relapse following radical prostatectomy (RP). We previously conducted three neoadjuvant androgen-deprivation therapy (ADT) trials prior to RP in unfavorable intermediate and high-risk disease.

Methods In this analysis, we report on the post-RP outcomes of a subset of patients enrolled on these studies. We conducted a pooled analysis of patients with available follow-up data treated on three neoadjuvant trials at three institutions. All patients received intense ADT prior to RP. The primary endpoint was time to biochemical recurrence (BCR). BCR was defined as a PSA ≥ 0.2 ng/mL or treatment with radiation or androgen-deprivation therapy for a rising PSA < 0.2 ng/mL.

Results Overall, 72 patients were included of whom the majority had a Gleason score ≥ 8 ($n = 46$, 63.9%). Following neoadjuvant therapy, 55.7% of patients ($n = 39/70$) had pT3 disease, 40% ($n = 28$) had seminal vesicle invasion, 12.9% ($n = 9$) had positive margins, and 11.4% ($n = 8$) had lymph node involvement. Overall, 11 (15.7%) had tumor measuring ≤ 0.5 cm, which included four patients (5.7%) with a pathologic complete response and seven (10.0%) with residual tumor measuring 0.1–0.5 cm. Compared to pretreatment clinical staging, 10 patients (14.3%) had pathologic T downstaging at RP. The median follow-up was 3.4 years. Overall, the 3-year BCR-free rate was 70% (95% CI 57%, 90%). Of the 15 patients with either residual tumor ≤ 0.5 cm or pathologic T downstaging, no patient experienced a recurrence.

Conclusion In this exploratory pooled clinical trials analysis, we highlight that neoadjuvant therapy prior to RP in unfavorable intermediate and high-risk patients may potentially have a positive impact on recurrence rates. Larger studies with longer follow-up periods are warranted to evaluate the impact of neoadjuvant hormone therapy on pathologic and long-term outcomes.

Introduction

Despite generally outstanding results for radical prostatectomy (RP), patients with high-risk prostate cancer (PC) have an increased risk of biochemical recurrence (BCR) and

Rana R. McKay, Bruce Montgomery, Adam S. Kibel, and Mary-Ellen Taplin contributed equally to this work.

✉ Mary-Ellen Taplin
Mary_Taplin@DFCI.harvard.edu

[1] Department of Medicine, Division of Hematology/Oncology, University of California San Diego, San Diego, CA, USA

[2] Department of Medicine, Division of Oncology, University of Washington, Seattle, WA, USA

[3] Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston MA, USA

[4] Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

[5] Department of Medicine, Division of Hematology/Oncology, Beth Israel Deaconess Medical Center, Boston, MA, USA

[6] Department of Urology, University of Washington, Seattle, WA, USA

[7] Department of Surgery, Division of Urology, Dana Farber/Brigham and Women's Cancer Center, Boston MA, USA

[8] Department of Urology, Beth Israel Deaconess Medical Center, Boston, MA, USA

[9] Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

PC mortality despite treatment [1]. Biochemical recurrence may not be indolent since approximately one-third of men with high-risk disease who suffer a BCR will die of PC within 10 years [2]. While adjuvant and salvage therapies can improve outcomes for patients with local recurrences, the overall relapse rate is still unacceptably high, in part due to occult systemic disease and radiation resistance. Consequently, novel strategies that integrate multimodality therapy are warranted to improve cure for high-risk patients.

Neoadjuvant systemic therapy is a widely accepted paradigm for the treatment of malignancies including breast [3], bladder [4, 5], and esophageal [6, 7]. Neoadjuvant therapy offers the potential for systemic control of microscopic metastases, while optimally treating the primary disease [8]. In some cases, neoadjuvant therapy may facilitate resection and provide prognostic information with an in vivo assessment of treatment sensitivity [8]. A key principal of neoadjuvant therapy is that local response correlates with long-term survival. In breast cancer, pathologic complete response (pCR) has been used as a surrogate for long-term survival resulting in FDA approval of pertuzumab [9]. Additionally, residual cancer burden (RCB), a method to quantify residual disease after neoadjuvant chemotherapy for breast cancer that incorporates number and size of nodal metastases and percent cellularity of the primary tumor bed, has been shown to correlate with long-term survival [10].

Historically, androgen-deprivation therapy (ADT) is the primary systemic therapy for men with PC [11]. The utilization of neoadjuvant ADT prior to RP was evaluated in the 1990's and while initially demonstrated improvements in the rate of organ-confined disease and decreased positive surgical margins, there was no benefit in recurrence rates [12–23]. These studies were underpowered to detect significant differences between disease-free survival (DFS) and overall survival (OS) given limited reporting of these endpoints, lack of long-term follow-up, and inclusion of primarily low and intermediate-risk patients [24].

These studies primarily utilized treatment with luteinizing hormone-releasing hormone (LHRH) agonizts and/or first-generation anti-androgens. Treatment with LHRH agonists and first-generation anti-androgens results in incomplete suppression of tissue androgen, which is hypothesized to be another possible explanation for the lack of efficacy of these former studies [25]. While serum androgens are reduced by approximately 90% with standard ADT, tissue androgens only decline by 75%, providing rationale for more complete androgen blockade [25].

The development of more potent hormonal agents provides the opportunity to investigate these therapeutic options in the neoadjuvant setting. In addition to LHRH suppression, further androgen receptor (AR) axis suppression can be achieved by targeting CYP17-mediated

Table 1 Summary of neoadjuvant trials

Study	Enrollment period	Patients enrolled	Selection criteria	Arms	Duration of neoadjuvant therapy	Primary endpoint
TAPS(27) (NCT00298155)	July 2006–December 2009	35	cT1-T3 AND PSA < 40 ng/dL AND Gleason 7–10	1: Goserelin + Dutasteride 2: Goserelin + Dutasteride + Bicalutamide 3: Goserelin + Dutasteride + Bicalutamide + Ketoconazole (1:1:1)	3-months	Prostate tissue DHT levels
Neo-Abi(26) (NCT00924469)	September 2009–June 2011	58	Positive biopsies ≥ 3 AND Gleason score ≥ 7 OR PSA > 10 ng/mL OR PSA velocity > 2 ng/mL/year	1: 12 weeks Abiraterone acetate/ 24 weeks LHRH agonist 2: 24 weeks Abiraterone acetate/ 24 weeks LHRH agonist (1:1)	24 weeks	Prostate tissue testosterone and DHT levels
Neo-Enza(28) (NCT01547299)	March 2012–November 2013	52	Positive biopsies ≥ 3 AND PSA > 10 ng/mL OR Gleason score ≥ 7 (4 + 3); T4 excluded	1: Enzalutamide 2: Enzalutamide + Leuprolide + Dutasteride (1:1)	6-months	Pathologic complete response rate

PSA prostate-specific antigen, *DHT* dihydrotestosterone, *LHRH* luteinizing hormone-releasing hormone

androgen synthesis (ketoconazole, abiraterone) or with AR inhibition (enzalutamide). Abiraterone and enzalutamide improve OS in metastatic castration-resistant PC. We hypothesized that intense ADT can improve outcomes in high-risk localized PC and have published three neoadjuvant studies utilizing these hormonal agents [26–28]. Herein, we report on the post-RP outcomes of patients with available follow-up data enrolled on these studies.

Patients and methods

Patients

We conducted a pooled analysis of patients treated on three neoadjuvant trials at three institutions: Dana-Farber/Brigham and Women's Cancer Center, University of Washington, and Beth Israel Deaconess Medical Center (Table 1). Post-RP follow-up, including frequency of clinic visits, prostate-specific antigen (PSA) and radiographic evaluations, was not predefined on the studies given funding restrictions. Given that long-term follow up after RP was not mandated, patients included were those with available PSA and follow-up data. Clinical, laboratory, and radiographic data following RP were obtained. The decision to initiate adjuvant or salvage therapy was at the discretion of the treating physician. Informed consent was obtained from all subjects. This study was approved by the Institutional Review Board at each institution.

Statistical analysis

The primary endpoint was time to BCR, defined as the time from RP to BCR, censored at the last PSA follow-up for those without progression. BCR was defined as a PSA ≥ 0.2 ng/mL, with a second confirmatory level ≥ 0.2 ng/mL, or treatment with salvage radiation therapy or ADT for a rising PSA that was < 0.2 ng/mL at the time of therapy initiation. A secondary endpoint included time to metastasis (TTM), defined as the time of RP to the first evidence of metastasis on imaging, censored at the date of last PSA or imaging follow-up for those without progression. The distributions of time to BCR or TTM were estimated using the Kaplan–Meier method.

Median time to BCR and BCR-free rate at 2 and 3 years along with 95% confidence interval (CI) were summarized in overall cohort and by pathological response groups. Two pathological outcomes were analyzed: (1) minimum residual disease (MRD) defined as tumor in the RP specimen measuring ≤ 0.5 cm, and (2) improved pathologic T stage compared to clinical staging defined by the American Joint Committee on Cancer (AJCC) staging system at baseline. Patients who had an improvement in T stage either between T stage categories or within T stage categories were counted as having downstaging. The subgroup analyses of BCR by pathological response groups were explorative with limited statistical power; no formal comparison was provided.

Time to testosterone recovery was estimated by the Kaplan–Meier method. The recovery time was calculated from the date of RP to testosterone > 200 ng/dL, or censored at the last sample date if testosterone had not reached a normal level. If patients received ADT prior to testosterone recovery, their time to testosterone recovery was censored at the date of ADT initiation.

We conducted a descriptive exploratory analysis to evaluate the predicted pathologic RP outcomes of matched patients with comparable high-risk features planned to undergo RP alone. Using the Memorial Sloan Kettering Cancer Center (MSKCC) pre-RP nomogram (https://www.mskcc.org/nomograms/prostate/pre-op), we used the baseline parameters of patients in our cohort to determine the predicted pathologic outcomes including extracapsular extension, seminal vesicle invasion, and lymph node involvement of RP alone. No formal test could be made for this descriptive comparison.

Results

Baseline characteristics

Overall, 72 patients (50% of those enrolled on the trials) were included (Table 2). The median PSA prior to neoadjuvant therapy was 8.3 ng/mL. The majority of patients had a Gleason score ≥ 8 ($n = 46$, 63.9%). Fifty-two patients (72.2%) had high-risk disease by NCCN criteria.

Pathologic RP outcomes

Of the 72 patients, 70 (97.2%) had pathologic data available (Table 3). Two patients discontinued study treatment early and subsequently received RP at outside hospitals. The majority of patients ($n = 39$, 55.7%; 95% CI: 43%, 68%) had pT3 disease at RP and eight patients (11.4%; 95% CI: 5%, 21%) had lymph node involvement. The rates of seminal vesicle involvement and positive margins were 40% ($n = 28$; 95% CI: 28–52%) and 12.9% ($n = 9$; 95% CI: 6%, 23%), respectively.

Overall, 11 (15.7%; 95% CI: 8%, 26%) had tumor measuring ≤ 0.5 cm at largest cross section dimension in the RP specimen, including four patients (5.7%) with a pCR and seven (10.0%) with residual tumor measuring 0.1–0.5 cm. Of the patients with residual tumor measuring ≤ 0.5 cm, eight (72.7%) were treated on the Neo-Abi trial and three (27.3%) on the Neo-Enza trial.

Table 2 Baseline patient and disease characteristics

	Current analysis cohort ($N = 72$)	Original trial cohorts					
		TAPS ($n = 35$)		Neo-Abi ($n = 58$)		Neo-Enza ($n = 52$)	
	N (%)	Included *N* (%)	Excluded *N* (%)	Included *N* (%)	Excluded *N* (%)	Included *N* (%)	Excluded *N* (%)
Total *N*	72	4	31	41	17	27	25
Institution							
BIDMC	7 (10)	—	—	—	—	—	—
DF/BWCC	48 (67)	—	—	—	—	—	—
UW	17 (24)	—	—	—	—	—	—
Gleason score							
Gleason 7	26 (36)	1 (25)	24 (77)	15(37)	3 (18)	10 (37)	10 (40)
3 + 4	5 (7)	—	—	—	—	—	—
4 + 3	21 (29)	—	—	—	—	—	—
Gleason 8–10	46 (64)	3 (75)	7 (23)	26(63)	14 (82)	17 (63)	15 (60)
3 + 5	3 (4)	—	—	—	—	—	—
4 + 4	18 (25)	—	—	—	—	—	—
4 + 5	16 (22)	—	—	—	—	—	—
5 + 4	6 (8)	—	—	—	—	—	—
5 + 5	3 (4)	—	—	—	—	—	—
Clinical T stage							
T1	20 (28)	1 (25)	9 (29)	13 (32)	3 (18)	6 (22)	8 (32)
T2	37 (51)	2 (50)	16 (52)	24 (59)	6 (35)	11 (41)	13 (52)
T3	12 (17)	1 (25)	6 (19)	3 (7)	7 (41)	8 (30)	4 (16)
Unknown	3 (4)	0	0	1 (2)	1 (6)	2 (7)	0
NCCN risk group							
	20 (28)	1 (25)	—	12 (29)	1 (6)	7 (26)	4 (16)
Intermediate							
High	52 (72)	3 (75)	—	29 (71)	16 (94)	20 (74)	21 (84)
	Median (IQR)	Median by treatment arm (range)	—	Median by treatment arm (range)	—	Median by treatment arm (range)	—
PSA at Baseline (ng/mL)	8.3 (5.0–14.2)	11.9/5.8/ 7.9 (-)	—	12.1/6.4 (2–316.6)	—	10.9/12.8 (0.6–61.1)	—
Median age at RP, years	59 (54–63)	62/66/60 (-)	—	55/60 (50–74)	—	61/60 (46–75)	—

—denotes not available

BIDMC Beth Israel Deaconess Medical Center, *DF/BWCC* Dana-Farber/Brigham and Women's Cancer Center, *UW* University of Washington, *NCCN* National Comprehensive Cancer Network, *NA* not available, *IQR* interquartile range, *PSA* prostate-specific antigen, *RP* radical prostatectomy

Compared to pretreatment clinical staging, ten patients (14.3%; 95% CI: 7%, 25%) had pathologic T downstaging at RP, including four patients (5.7%) with downstaging from T3 to pT2, four patients (5.7%) with downstaging from T1/T2 to pT0 and two patients (2.9%) with change in subcategories. Six patients achieved both tumor measuring ≤ 0.5 cm and pathologic T downstaging. Overall, 15 patients (20.8%; 95% CI: 13%, 33%) had either tumor measuring ≤ 0.5 cm or pathologic T downstaging at RP.

MSKCC pre-RP nomogram prediction

The predicted rates of extracapsular extension, seminal vesicle invasion, and lymph node involvement for matched

Table 3 Pathologic outcomes at radical prostatectomy

	Current analysis cohort ($n = 70$)		Original trial cohorts					
			TAPS ($n = 32$)		Neo-Abi ($n = 56$)		Neo-Enza ($n = 48$)	
	N	%	*N*	%	*N*	%	*N*	%
Pathologic T stage								
pT0	4	5.7	2	6.3	4	7.1	1	2.1
pT2	27	38.6	21	65.6	22	39.3	15	31.3
pT3	39	55.7	9	28.1	30	53.6	32	66.7
Pathologic T down-stage[a]								
Yes	10	14.3	—	—	—	—	—	—
No	57	81.4	—	—	—	—	—	—
Unknown	3	4.3	—	—	—	—	—	—
Pathologic N Stage								
N0	61	87.1	—	—	46	82.1	41	85.4
N1	8	11.4	—	—	10	17.9	7	14.6
Unknown	1	1.4	—	—	0	0	0	0
Positive margin								
Yes	9	12.9	—	—	8	14.3	9	18.8
No	61	87.1	—	—	48	85.7	39	81.3
Seminal vesicle involvement								
Yes	28	40.0	5	15.6	17	30.4	16	33.3
No	42	60.0	27	84.4	39	69.6	32	66.7
Largest cross section dimension								
≤0.5 cm	11	15.7	—	—	—	—	—	—
>0.5 cm	55	78.6	—	—	—	—	—	—
Unknown	4	5.7	—	—	—	—	—	—
Pathologic complete response								
Yes	4	5.7	2	6.3	4	7.1	1	2.1
No	66	94.3	30	93.7	52	92.9	47	97.9

Improved from T1c to pT0 ($N = 2$), T2a to pT0 ($N = 1$), T2b to pT2a ($N = 1$), T2c to pT0 ($N = 1$), T3 to pT2 ($N = 1$), T3a to pT2a ($N = 2$), T3a to pT2c ($N = 1$), T3b to pT3a ($N = 1$)

—denotes not available

[a]Downstaging of clinical T stage as defined by AJCC staging system at diagnosis to pathologic T stage at radical prostatectomy

patients undergoing RP alone were 78%, 23%, and 25%, respectively. The predicted 3-year BCR-free rate was 50%.

Time to BCR, TTM, and OS

Overall, the median follow-up post-RP was 3.4 years (range 0.1–7.0): 5.7 years for TAPS, 4.3 years for Neo-Abi, and 2.6 years for Neo-Enza. Twenty-three patients had a BCR and median time to BCR was 5.1 years (95% CI: 4.4, not reached) (Fig. 1a). The 2-year BCR-free rate was 75% (95% CI: 63%, 84%) and 3-year rate was 70% (95% CI: 57%, 80%). Five

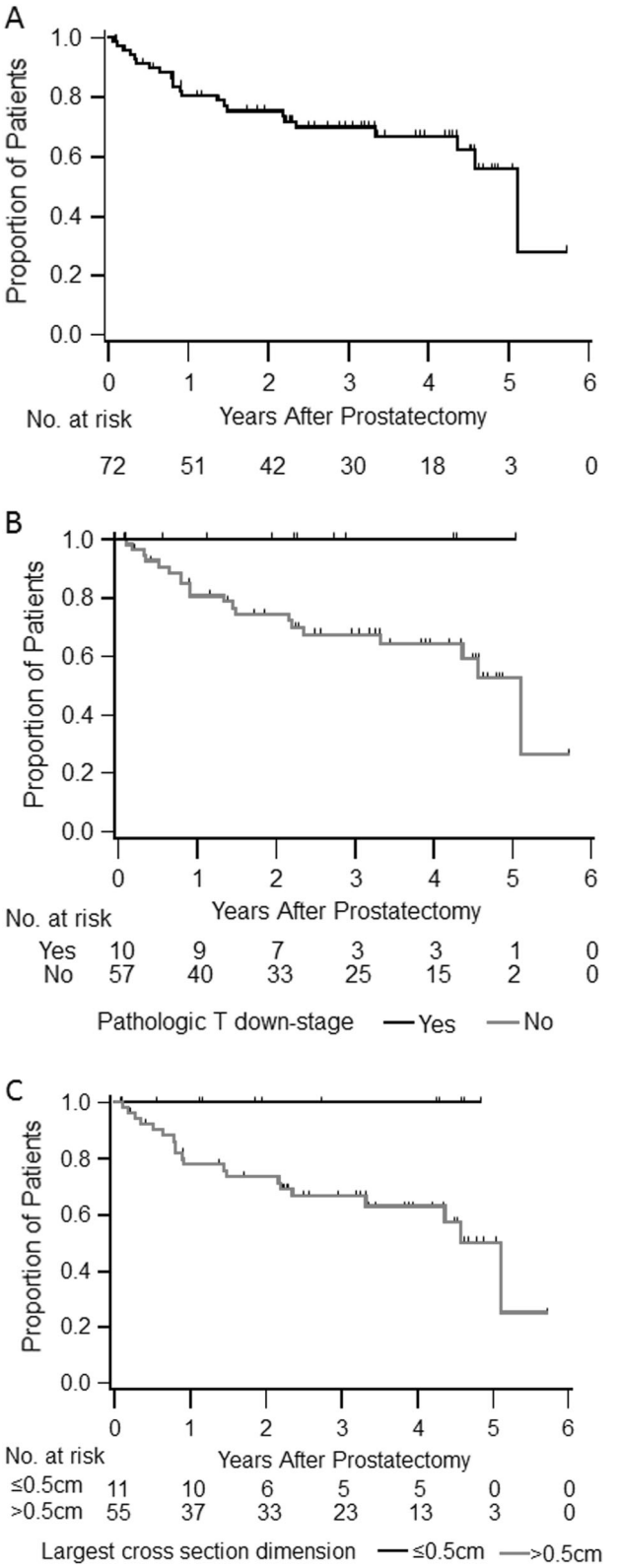


Fig. 1 Kaplan–Meier estimates of BCR (panel **a**) for the total cohort. Time to BCR by pathologic T downstaging (yes vs. no) (**b**) and largest cross section dimension (≤ 0.5 cm or > 0.5 cm) (**c**)

Table 4 Time to BCR in the total cohort and by pathologic parameters

Pathologic parameter	*N.*[a]	Number of events	Median, year (95% CI)	BCR free rate	
				2-Year (95% CI)	3-Year(95% CI)
All patients	72	23	5.1 (4.4, NR)	75% (63%, 84%)	70% (57%, 80%)
Pathologic T downstaging					
Yes	10	0	NR	100%	100%
No	57	20	5.1 (3.3, NR)	74% (60%, 84%)	67% (52%, 79%)
Largest cross section dimension					
≤0.5 cm	11	0	NR	100%	100%
>0.5 cm	55	20	5.1 (3.3, NR)	74% (60%, 84%)	67% (52%, 79%)

NR not reached

[a]Exclude patients who did not have pathologic parameters because surgery was done at outside hospitals or tumor measures (i.e., T stage or Largest Cross Section Dimension) were not available from the original trials

patients (6.9%) developed metastases and median TTM was not reached. The 3-year metastasis-free survival was 95% (95% CI: 0.86, 0.98). Overall, there was one death from PC and 3-year OS rate was 98% (95% CI: 88%, 100%).

Time to BCR by pathologic parameters

In an exploratory analysis evaluating time to BCR by pathologic T downstaging, no patient with pathologic T downstaging ($n = 10$) had a BCR and median time to BCR was not reached (Table 4, Fig. 1b). Similarly, there were no recurrences in patients with a residual tumor ≤ 0.5 cm ($n = 11$) (Table 4, Fig. 1c). Median follow-up was 2.7 (range 0.6, 5.0) years in those with residual tumor ≤ 0.5 cm or pathologic T downstaging ($n = 15$).

Testosterone recovery

Post-RP testosterone data were available for 47 patients from two institutions. Overall, median time to testosterone recovery from RP was 4.0 months (95% CI: 3.4–4.9). The cumulative testosterone recovery rate was 31% (95% CI: 20%, 47%) by 3-months, 77% (95% CI: 63, 88%) by 6-months, and 88% (76, 96%) by 1-year, respectively.

Forty out of 47 patients had testosterone recovery, of whom 27 (67%) were BCR-free at last follow-up. The BCR-free rate at 2-years post testosterone recovery was 73% (95% CI: 55%, 85%). Four patients with low testosterone were lost to follow-up and were censored at the last testosterone test date. Three patients who received ADT prior to testosterone recovery were censored at time of ADT initiation.

Discussion

This exploratory analysis was designed to investigate the post-RP outcomes of patients treated with intense neoadjuvant androgen deprivation. We demonstrate that at a median of three years following RP, 70% of patients remain disease free. Furthermore, no patient with pathologic T downstaging or residual tumor ≤ 0.5 cm experienced a recurrence. While our series is limited by the small number of patients and low failure events, neoadjuvant therapy prior to RP in unfavorable intermediate and high-risk patients may potentially have a positive impact on recurrence rates. These data are hypothesis generating and larger randomized studies with longer follow-up are needed to evaluate the benefit of neoadjuvant hormone therapy.

Currently, RP alone is insufficient for many patients with high-risk PC. Historic trials have evaluated the role of neoadjuvant hormonal therapy. The largest randomized trial included 547 men with cT1-T2 randomized to leuprolide and flutamide for three or eight months before RP [20]. Eight months of therapy was associated with improved preoperative PSA, lower positive surgical margin rate, and higher organ-confined disease rate [20]. Although the pCR rate was higher in the eight month group compared to the three-month group (9.3% vs. 5.1%), this was not statistically significant [20]. A meta-analysis including ten studies of neoadjuvant ADT prior to RP demonstrated statistically significant improvements in pathologic parameters at RP, however, these did not correspond to improved DFS or OS [24].

The more contemporary clinical trials included in this meta-analysis evaluate more potent androgen blockade beyond LHRH therapy and first-generation anti-androgens. This is the first report of the post-RP outcomes data of patients enrolled on these studies. While neoadjuvant ADT remains under investigation, our data highlight that a subset of patients may have a favorable response to treatment. This is consistent with recent data from the Systemic Therapy in Advancing or Metastatic PC: Evaluation of Drug Efficacy (STAMPEDE) trial evaluating abiraterone in patients never previously treated with hormone therapy [29]. Of the 1917

patients randomized, 27% had newly diagnosed high-risk locally advanced disease [29]. Overall, abiraterone added to ADT was associated with a 37% improvement in OS compared to ADT alone (hazard ratio (HR) 0.63; 95% CI: 0.52–0.76, $p < 0.001$) [29]. The benefit of abiraterone was seen in those with non-metastatic (HR = 0.71) and metastatic disease (HR = 0.65) [29].

Additionally, there is an increasing interest in surgery as part of an integrated multimodal treatment paradigm for patients with locally advanced or oligometastatic PC [30]. Radical surgery to remove the primary in metastatic disease has been associated with improved survival in several solid tumors including colorectal [31] and renal cell carcinoma [32]. With regards to PC, though prospective studies are lacking, a number of retrospective studies have demonstrated the potential benefit of RP in patients with advanced disease [30]. A Surveillance Epidemiology and End Results-based study compared the survival of 8185 men with metastatic PC receiving RP, brachytherapy or no local treatment, and demonstrated an improvement in 5-year OS with local treatment [33]. The safety and efficacy of RP in very-high risk or oligometastatic PC is being investigated in a single arm phase 1/2 clinical trial (NCT02971358). Additional randomized trials will be necessary to evaluate the role of multimodal therapy for locally advanced or metastatic PC.

In our cohort, 11% of patients were observed to have microscopic lymph node involvement at RP. These results are comparable to historic studies documenting rates of nodal involvement at ~10% in high-risk patients undergoing RP [34]. Additionally, in the exploratory analysis evaluating predicted pathologic outcomes of matched patients having undergone RP alone, the predicted rate of nodal involvement was 25%. Although patients did not have clinical lymph node involvement at baseline in our cohort, whether microscopic lymph node involvement was present at baseline is unknown. Direct comparisons cannot be made between these analyses, which highlight the differences between clinical and pathologic staging.

The impact of the pathologic response on long-term outcomes in PC has not been established. In our study, the pCR rate was low, though a subset of patients experienced pathologic T downstaging or MRD. Interestingly, there were no recurrences in these patients. It is possible that pathologic response may correlate with long-term clinical benefit, however, the duration of follow-up was short. Our analysis was exploratory and not powered to investigate the association of pathologic and survival outcomes.

In this analysis, we defined MRD as a residual tumor ≤ 0.5 cm. However, this definition does not account for tumor volume and cellularity. In the Neo-Abi trial, we investigated the significance of MRD defined as RCB (tumor volume corrected for tumor cellularity) ≤ 0.25 cm^3 [26]. The rates of RCB ≤ 0.25 cm^3 ranged from 44–52%. Similar results were seen on the Neo-Enza trial with rates of RCB ≤ 0.25 cm^3 of 36–74%. Consensus criteria for the measurement and reporting of pCR and MRD are important in the planning and interpretation of future neoadjuvant trials.

Despite more effective blockade of the androgen axis, the rate of testosterone recovery in our cohort was 85% and median time to testosterone recovery was 4 months. The short recovery time may be related to the young age of our population. We anticipate additional recovery with longer follow-up. Historic trials of neoadjuvant ADT evaluating variable durations of ADT ranging from 3–8 months did not report on testosterone recovery. For reference, we previously evaluated the efficacy of a LHRH agonist, bicalutamide with or without bevacizumab administered for six months in recurrent PC [35]. The rate of testosterone recovery in the ADT only cohort of this study was 71% and median time to testosterone recovery was 10.1 months. Although direct comparisons cannot be made, it appears that testosterone recovery following 6-months of potent androgen blockade was not inferior to that with standard ADT.

In our cohort, the 3-year BCR-free rate was 70% post-RP with eight patients receiving adjuvant radiation therapy or ADT. Using the MSKCC pre-RP nomogram, the predicted 3-year BCR-free rate was 50% for matched patients undergoing RP alone. Numerous questions remain regarding the long-term impact of neoadjuvant therapy on rates of BCR, need for salvage therapy, metastasis development, and OS. Although promising, the significance of our observation on BCR is indeterminate and the benefits can only truly be determined by a phase 3 trial.

Despite neoadjuvant therapy, the majority of patients had residual disease, underscoring the need to identify and target resistance in these patients. We previously demonstrated that persistent intraprostatic tissue androgens and continued AR activity in residual tumor cells may drive resistance [26, 27]. These data suggest that more potent AR inhibition or potentially longer therapy may be warranted. We are investigating these questions in two subsequent neoadjuvant studies. One study, which recently completed accrual, is evaluating the combination of abiraterone and enzalutamide (NCT02268175). The other study, currently open to accrual, is a two-part phase 2 study evaluating neoadjuvant and adjuvant abiraterone and apalutamide, a potent AR antagonist (NCT02903368). Additional correlative analyses are evaluating the genomic and expression profiles of baseline prostate biopsy and RP tissue for biomarkers of exceptional responders and resistance.

This post-hoc exploratory analysis has several limitations. Although patients were enrolled on prospective clinical trials, post-RP follow-up was variable between patients and data were collected retrospectively. Direct

comparisons between the three trials is limited given differences in baseline patient and disease characteristics and small sample size. The endpoint of T downstaging at RP is weak given that clinical T stage at baseline was compared to pathologic T stage at RP. The analysis evaluating predicted pathologic outcomes is limited and direct comparisons cannot be made to our cohort. Furthermore, the endpoint of 3-year BCR is short and number of failure events was low.

Our subset analysis from three contemporary multicenter trials evaluating neoadjuvant intense ADT, demonstrates a favorable BCR compared to MSKCC nomogram predicted BCR. Ultimately, a randomized phase 3 study will be necessary to challenge the current treatment paradigm for men with unfavorable intermediate and high-risk disease and prove the value of neoadjuvant/adjuvant intense ADT. The development of such a study poses challenges in terms of the best choice of an intermediate clinical endpoint that is a surrogate for OS and funding. Our preliminary data support that pCR plus MRD (≤ 0.5 cm tumor or RCB $< 25\%$) could be an endpoint that will correlate with BCR and ultimately freedom from metastasis. Despite these challenges, conduct of future neoadjuvant/adjuvant studies is needed to improve the current standard of care for these patients.

Acknowledgements We acknowledge the patients and families who participated in trials included in this analysis.

Funding This work was supported by Janssen, Medivation, Prostate Cancer Foundation, A. David Mazzone Award Program, and the Fairweather Family Fund. The funding sponsors were not involved in the design of study, data collection and analysis, and manuscript preparation.

Compliance with ethical standards

Conflict of interest RRM received research funding from Bayer and Pfizer. QDT is supported by an unrestricted educational grant from the Vattikuti Urology Institute, a Clay Hamlin Young Investigator Award from the Prostate Cancer Foundation and a Genentech BioOncology Career Development Award from the Conquer Cancer Foundation of the American Society of Clinical Oncology. RBM received research support from Jansen, Medivation and ESSA. ASK receives advisory board honorarium from Janssen, Bayer, and Sanofi-Aventis. MET receives research funding and advisory board honorarium from Janssen, Medivation.

References

1. Eggener SE, Scardino PT, Walsh PC, Han M, Partin AW, Trock BJ, et al. Predicting 15-year prostate cancer specific mortality after radical prostatectomy. J Urol. 2011;185:869–75.
2. Brockman JA, Alanee S, Vickers AJ, Scardino PT, Wood DP, Kibel AS, et al. Nomogram predicting prostate cancer-specific mortality for men with biochemical recurrence after radical prostatectomy. Eur Urol. 2015;67:1160–7.
3. Mauri D, Pavlidis N, Ioannidis JP. Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. J Natl Cancer Inst. 2005;97:188–94.
4. Meeks JJ, Bellmunt J, Bochner BH, Clarke NW, Daneshmand S, Galsky MD, et al. A systematic review of neoadjuvant and adjuvant chemotherapy for muscle-invasive bladder cancer. Eur Urol. 2012;62:523–33.
5. Advanced Bladder Cancer Meta-analysis C. Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis. Lancet. 2003;361:1927–34.
6. Sjoquist KM, Burmeister BH, Smithers BM, Zalcberg JR, Simes RJ, Barbour A, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol. 2011;12:681–92.
7. Kidane B, Coughlin S, Vogt K, Malthaner R. Preoperative chemotherapy for resectable thoracic esophageal cancer. Cochrane Database Syst Rev. 2015:CD001556. Issue 5.
8. McKay RR, Choueiri TK, Taplin ME. Rationale for and review of neoadjuvant therapy prior to radical prostatectomy for patients with high-risk prostate cancer. Drugs. 2013;73:1417–30.
9. Gianni L, Pienkowski T, Im YH, Roman L, Tseng LM, Liu MC, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol. 2012;13:25–32.
10. Peintinger F, Sinn B, Hatzis C, Albarracin C, Downs-Kelly E, Morkowski J, et al. Reproducibility of residual cancer burden for prognostic assessment of breast cancer after neoadjuvant chemotherapy. Mod Pathol. 2015;28:913–20.
11. Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and androgen injection on serum phosphatases in metastatic carcinoma of the prostate. CA Cancer J Clin. 1972;22:232–40.
12. Yee DS, Lowrance WT, Eastham JA, Maschino AC, Cronin AM, Rabbani F. Long-term follow-up of 3-month neoadjuvant hormone therapy before radical prostatectomy in a randomized trial. BJU Int. 2010;105:185–90.
13. van der Kwast TH, Tetu B, Candas B, Gomez JL, Cusan L, Labrie F. Prolonged neoadjuvant combined androgen blockade leads to a further reduction of prostatic tumor volume: three versus six months of endocrine therapy. Urology. 1999;53:523–9.
14. Soloway MS, Pareek K, Sharifi R, Wajsman Z, McLeod D, Wood DP Jr., et al. Neoadjuvant androgen ablation before radical prostatectomy in cT2bNxMo prostate cancer: 5-year results. J Urol. 2002;167:112–6.
15. Selli C, Montironi R, Bono A, Pagano F, Zattoni F, Manganelli A, et al. Effects of complete androgen blockade for 12 and 24 weeks on the pathological stage and resection margin status of prostate cancer. J Clin Pathol. 2002;55:508–13.
16. Schulman CC, Debruyne FM, Forster G, Selvaggi FP, Zlotta AR, Witjes WP. 4-Year follow-up results of a European prospective randomized study on neoadjuvant hormonal therapy prior to radical prostatectomy in T2-3N0M0 prostate cancer. European Study Group on Neoadjuvant Treatment of Prostate Cancer. Eur Urol. 2000;38:706–13.
17. Prezioso D, Lotti T, Polito M, Montironi R. Neoadjuvant hormone treatment with leuprolide acetate depot 3.75mg and cyproterone acetate, before radical prostatectomy: a randomized study. Urol Int. 2004;72:189–95.
18. Labrie F, Cusan L, Gomez JL, Diamond P, Suburu R, Lemay M, et al. Neoadjuvant hormonal therapy: the Canadian experience. Urology. 1997;49:56–64.
19. Klotz LH, Goldenberg SL, Jewett MA, Fradet Y, Nam R, Barkin J, et al. Long-term followup of a randomized trial of 0 versus 3 months of neoadjuvant androgen ablation before radical prostatectomy. J Urol. 2003;170:791–4.

20. Gleave ME, Goldenberg SL, Chin JL, Warner J, Saad F, Klotz LH, et al. Randomized comparative study of 3 versus 8-month neoadjuvant hormonal therapy before radical prostatectomy: biochemical and pathological effects. J Urol. 2001;166:500–6. discussion6-7
21. Fair WR, Rabbani F, Bastar A, Betancourt J. Neoadjuvant hormone therapy before radical prostatectomy: update on the Memorial Sloan-Kettering Cancer Center Trials. Mol Urol. 1999;3:253–60.
22. Dalkin BL, Ahmann FR, Nagle R, Johnson CS. Randomized study of neoadjuvant testicular androgen ablation therapy before radical prostatectomy in men with clinically localized prostate cancer. J Urol. 1996;155:1357–60.
23. Aus G, Abrahamsson PA, Ahlgren G, Hugosson J, Lundberg S, Schain M, et al. Three-month neoadjuvant hormonal therapy before radical prostatectomy: a 7-year follow-up of a randomized controlled trial. BJU Int. 2002;90:561–6.
24. Shelley MD, Kumar S, Wilt T, Staffurth J, Coles B, Mason MD. A systematic review and meta-analysis of randomised trials of neo-adjuvant hormone therapy for localised and locally advanced prostate carcinoma. Cancer Treat Rev. 2009;35:9–17.
25. Mostaghel EA, Page ST, Lin DW, Fazli L, Coleman IM, True LD, et al. Intraprostatic androgens and androgen-regulated gene expression persist after testosterone suppression: therapeutic implications for castration-resistant prostate cancer. Cancer Res. 2007;67:5033–41.
26. Taplin ME, Montgomery B, Logothetis CJ, Bubley GJ, Richie JP, Dalkin BL, et al. Intense androgen-deprivation therapy with abiraterone acetate plus leuprolide acetate in patients with localized high-risk prostate cancer: results of a randomized phase II neoadjuvant study. J Clin. Oncol. 2014;32:3705–15.
27. Mostaghel EA, Nelson PS, Lange P, Lin DW, Taplin ME, Balk S, et al. Targeted androgen pathway suppression in localized prostate cancer: a pilot study. J Clin. Oncol. 2014;32:229–37.
28. Montgomery B, Tretiakova MS, Joshua AM, Gleave ME, Fleshner N, Bubley GJ et al. Neoadjuvant enzalutamide prior to prostatectomy. Clin Cancer Res. 2017;23:2169-2176.
29. James ND, de Bono JS, Spears MR, Clarke NW, Mason MD, Dearnaley DP, et al. Abiraterone for prostate cancer not previously treated with hormone therapy. N Engl J Med. 2017;377:338–51.
30. Tosoian JJ, Gorin MA, Ross AE, Pienta KJ, Tran PT, Schaeffer EM. Oligometastatic prostate cancer: definitions, clinical outcomes, and treatment considerations. Nat Rev Urol. 2017;14:15–25.
31. Temple LK, Hsieh L, Wong WD, Saltz L, Schrag D. Use of surgery among elderly patients with stage IV colorectal cancer. J Clin Oncol 2004;22:3475–84.
32. Mickisch GH, Garin A, van Poppel H, de Prijck L, Sylvester R, European Organisation for R et al. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. Lancet. 2001;358:966–70.
33. Culp SH, Schellhammer PF, Williams MB. Might men diagnosed with metastatic prostate cancer benefit from definitive treatment of the primary tumor? A SEER-based study. Eur Urol. 2014;65:1058–66.
34. Pierorazio PM, Gorin MA, Ross AE, Feng Z, Trock BJ, Schaeffer EM, et al. Pathological and oncologic outcomes for men with positive lymph nodes at radical prostatectomy: The Johns Hopkins Hospital 30-year experience. Prostate. 2013;73:1673–80.
35. McKay RR, Zurita AJ, Werner L, Bruce JY, Carducci MA, Stein MN, et al. A Randomized Phase II trial of short-course androgen deprivation therapy with or without bevacizumab for patients with recurrent prostate cancer after definitive local therapy. J Clin Oncol. 2016;34:1913–20.

EUROPEAN UROLOGY 73 (2018) 687–693

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Prostate Cancer

Editorial by Rahul Aggarwal on pp. 694–695 of this issue

Clinical Outcome of Prostate Cancer Patients with Germline DNA Repair Mutations: Retrospective Analysis from an International Study

Joaquin Mateo[a,b,c,†], *Heather H. Cheng*[d,e,†], *Himisha Beltran*[f,†], *David Dolling*[a], *Wen Xu*[g], *Colin C. Pritchard*[d,e], *Helen Mossop*[a], *Pasquale Rescigno*[a,b], *Raquel Perez-Lopez*[a,b,c], *Verena Sailer*[f], *Michael Kolinsky*[a,b], *Ada Balasopoulou*[a], *Claudia Bertan*[a], *David M. Nanus*[f], *Scott T. Tagawa*[f], *Heather Thorne*[g,h], *Bruce Montgomery*[d,e], *Suzanne Carreira*[a], *Shahneen Sandhu*[g], *Mark A. Rubin*[f,i,‡], *Peter S. Nelson*[d,e,‡], *Johann S. de Bono*[a,b,‡,*]

[a] *The Institute of Cancer Research, London, UK;* [b] *The Royal Marsden NHS Foundation Trust, London, UK;* [c] *Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain;* [d] *University of Washington, Seattle, WA, USA;* [e] *Fred Hutchinson Cancer Research Center, Seattle, WA, USA;* [f] *Weill Cornell Medical College, New York, NY, USA;* [g] *The Sir Peter MacCallum Department of Oncology, The University of Melbourne, Melbourne, Australia;* [h] *Kathleen Cuningham Consortium for Research into Familial Breast Cancer (kConFab), Research Department, Peter MacCallum Cancer Centre, Melbourne, Australia;* [i] *University of Bern, Bern, Switzerland*

Article info

Article history:
Accepted January 9, 2018

Associate Editor:
James Catto

Keywords:
Biomarkers
BRCA
DNA repair
Genomics
Germline
Prostate cancer
Precision medicine

EU ACME
www.eu-acme.org/europeanurology

Please visit www.eu-acme.org/europeanurology to answer questions on-line. The EU-ACME credits will then be attributed automatically.

Abstract

Background: Germline DNA damage repair gene mutation (gDDRm) is found in >10% of metastatic prostate cancer (mPC). Their prognostic and predictive impact relating to standard therapies is unclear.
Objective: To determine whether gDDRm status impacts benefit from established therapies in mPC.
Design, setting, and participants: This is a retrospective, international, observational study. Medical records were reviewed for 390 mPC patients with known gDDRm status. All 372 patients from Royal Marsden (UK), Weill-Cornell (NY), and University of Washington (WA) were previously included in a prevalence study (Pritchard, NEJM 2016); the remaining 18 were g*BRCA1/2*m carriers, from the kConFab consortium, Australia.
Outcome measurements and statistical analysis: Response rate (RR), progression-free survival (PFS), and overall survival (OS) data were collected. To account for potential differences between cohorts, a mixed-effect model (Weibull distribution) with random intercept per cohort was used.
Results and limitations: The gDDRm status was known for all 390 patients (60 carriers of gDDRm [gDDRm+], including 37 g*BRCA2*m, and 330 cases not found to carry gDDRm [gDDRm–]); 74% and 69% were treated with docetaxel and abiraterone/enzalutamide, respectively, and 36% received PARP inhibitors (PARPi) and/or platinum. Median OS from castration resistance was similar among groups (3.2 vs 3.0 yr, $p = 0.73$). Median docetaxel PFS for gDDRm+ (6.8 mo) was not significantly different from that for gDDRm– (5.1 mo), and RRs were similar (gDDRm+ = 61%; gDDRm– = 54%). There were no significant differences in median PFS and RR on first-line abiraterone/enzalutamide (gDDRm+ = 8.3 mo, gDDRm– = 8.3 mo; gDDRm+ = 46%, gDDRm– = 56%). Interaction test for PARPi/platinum and gDDRm+ resulted in an OS adjusted hazard ratio of 0.59 (95% confidence interval 0.28–1.25; $p = 0.17$). Results are limited by the retrospective nature of the analysis.
Conclusions: mPC patients with gDDRm appeared to benefit from standard therapies similarly to the overall population; prospective studies are ongoing to investigate the impact of PARPi/platinum.
Patient summary: Patients with inherited DNA repair mutations benefit from standard therapies similarly to other metastatic prostate cancer patients.

† These authors contributed equally.
‡ These authors are co-senior authors of the study.
* Corresponding author. Division of Clinical Studies, The Institute of Cancer Research, Drug Development Unit, The Royal Marsden NHS Foundation Trust, Downs Rd, Sutton, Surrey SM2 5PT, UK.
E-mail address: johann.de-bono@icr.ac.uk (J.S. de Bono).

https://doi.org/10.1016/j.eururo.2018.01.010

Check for updates

1. Introduction

Inherited mutations in DNA damage repair (DDR) genes associate with an increased risk of developing prostate, breast, ovarian, and other cancers [1,2]. We previously described enrichment of such mutations in metastatic prostate cancer (mPC), with 11.8% of these men harbouring germline DNA damage repair gene mutation (gDDRm) [3]. Mutations in *BRCA2* were most prevalent (5.3%), with these data leading to a change in National Comprehensive Cancer Network (NCCN) guidelines, now recommending germline testing for all men with mPC [4]. Studies in mPC as well as in other diseases support tailored therapeutic approaches for this molecularly defined subset of patients [5–8].

Characterisation of the genomic landscape of prostate cancer has led to the identification of clinically actionable molecular alterations [9,10]. This renders an opportunity for a new classification of this common disease, beyond traditional anatomical and histological considerations, based on the prognostic and predictive significance of some of these alterations for treatment stratification.

Prior studies stated the role of germline *BRCA2* mutations are an independent poor prognostic factor for localised prostate cancer, associated with a more aggressive phenotype, increased rates of developing metastatic disease, and shorter survival from the disease [11,12]. However, when focusing on patients with mPC, the prognostic and predictive roles of gDDRm are unclear. Prior case series have reported conflicting data with regard to the relative benefit derived for patients carrying gDDRm from standard of care therapies (taxanes, abiraterone acetate, enzalutamide) [13–15].

Herein, we retrospectively reviewed the clinical outcome of mPC patients with and without gDDRm. We included 372 patients from three institutions enrolled in a previously published prevalence study of gDDRm (Royal Marsden, UK; Weill-Cornell, NY; University of Washington, WA); in order to increase the number of gDDRm carriers in this analysis, we included an additional cohort of 18 known g*BRCA1/2*m carriers with mPC from the kConFab consortium (Australia).

2. Patients and methods

All patients included had previously been tested for gDDRm. Germline mutations were called based on a panel of 20 genes summarised in Supplementary Table 1. For all the 372 cases from the three UK and US sites, these data had been published in a prior report, including sequencing and bioinformatics methodology [3]. In the original study, patients were not selected on the basis of family history, age, or any knowledge of genetic background. The remaining 18 patients were an independent cohort of known germline *BRCA1/2* germline mutation carriers from Australia. Patient medical records were retrospectively reviewed, and patients had received treatment according to local guidelines. Baseline characteristics (demographic characteristics, age, Gleason score, prostate-specific antigen [PSA] and presence of metastatic disease at diagnosis, treatment exposure, and survival data) were collected. Response data (defined as a 50% PSA fall from baseline and/or radiological response according to RECIST) and progression-free survival (PFS; defined as the time from start of a treatment to RECIST/PSA progression or start of a new therapy for clinical progression) for abiraterone, enzalutamide, and docetaxel were annotated.

To account for potential differences between the cohorts, a mixed-effect parametric survival model (Weibull distribution) with random intercept per cohort was used to study correlations with clinical outcome. Multivariate analyses adjusted for age, Gleason score, metastatic disease at diagnosis, and prior radical treatment at diagnosis (either radical prostatectomy or radiotherapy). Fisher's exact test was used to study response rates to each therapy. A test for interaction was pursued for an exploratory subgroup analysis assessing the impact of PARP inhibitors (PARPi) and/or platinum therapy on patient outcome. Kaplan–Meier curves were used to represent time to event data.

3. Results

3.1. Baseline characteristics and treatment exposure

Clinical data were available for 390 patients including 330 not found to carry gDDRm (gDDRm–) and 60 cases with presence of gDDRm (gDDRm+). The distribution of genes mutated per case within the gDDRm+ group was as follows: *BRCA2*: 37; *ATM*: seven; *CHEK2*: four; *BRCA1*, *PALB2*, *RAD51D*: two each; others: seven (one patient had both *ATM* and *CHEK2* mutations; Supplementary Tables 2 and 3). There were no significant differences in baseline characteristics based on gDDRm status (Table 1), including age at diagnosis (median of 62.6 vs 64.9 yr for gDDRm+ vs gDDRm–). Overall, 74% and 69% of patients received, respectively, docetaxel and novel androgen receptor signalling inhibitors (ARSIs: abiraterone acetate, enzalutamide) for metastatic castration-resistant prostate cancer (mCRPC). Based on the cross resistance demonstrated between abiraterone acetate and enzalutamide, in this analysis we considered only the first exposure to either abiraterone acetate or enzalutamide. Of note, 28/60 (47%) gDDRm+ and 113/330 (34%) gDDRm– patients also received treatment with PARPi and/or platinum chemotherapy, treatments that are not currently routinely used for prostate cancer care, reflecting the research focus of the involved academic groups.

3.2. Prognosis of patients with gDDRm

Overall survival (OS) was similar in the two subgroups, with 296 death events (75% of the study population), median OS from castration resistance was 3.0 yr for gDDRm+ (interquartile range [IQR] 2.4–5.6), 3.0 yr for g*BRCA2*+ (IQR 2.5–5.4), and 3.2 yr for gDDRm– (IQR 1.7–5.5; log-rank test $p = 0.73$). In multivariate analysis, age at diagnosis (per 10 yr older, adjusted hazard ratio [aHR] 1.45, 95% confidence interval [CI] 1.21–1.73; $p < 0.001$), and Gleason score ≥ 8 (aHR 1.54, 95% CI 1.16–2.04; $p = 0.003$), but not germline mutations (aHR 0.93, 95% CI 0.63–1.37; $p = 0.72$) were associated with worse survival. When looking specifically at the impact of germline *BRCA2* mutations, these were also not associated with a significantly different prognosis (aHR 0.83, 95% CI 0.50–1.36, $p = 0.45$; Table 2 and Fig. 1).

3.3. gDDRm and docetaxel

On docetaxel chemotherapy, gDDRm did not associate with significantly different PFS (HR 0.86, 95% CI 0.61–1.20, $p = 0.37$); similar results were observed when evaluating

Table 1 – Baseline characteristics of the study population (*n* = 390)

	Patients with any germline mutation (*n* = 60)		Patients without germline mutation (*n* = 330)		*p* value [a]
	N	%	*N*	%	
Gleason score					
5–7	15	28.9	105	37.5	0.27
8–10	37	71.2	175	62.5	
Metastatic disease at diagnosis					
No	34	58.6	173	53.7	0.57
Yes	24	41.4	149	46.3	
Received radical treatment					
No	22	36.7	140	42.4	0.48
Yes	38	58.5	190	57.6	
Docetaxel					
No	16	26.7	88	26.7	1.00
Yes	44	73.3	242	73.3	
Abiraterone and/or enzalutamide					
No	18	30	101	30.6	1.00
Yes	42	70	229	69.4	
PARPi and/or platinum					
No	32	53.3	217	65.8	0.08
Yes	28	46.7	113	34.2	
Radium-223					
No	52	86.7	296	90.2	0.37
Yes	8	13.3	32	9.8	
	Median	Q1–Q3	Median	Q1–Q3	*p* value [b]
Age at diagnosis (yr)	62.6	55.3–66.2	62.4	57.7–68.5	0.24
PSA (ng/dl)	17.2	7.7–109.6	33.0	9.8–148.3	0.34

PARPi = PARP inhibitors; PSA = prostate-specific antigen.

[a] Fisher's exact test.

[b] Wilcoxon rank sum test.

germline *BRCA2* mutation carriers alone (HR 0.96, 95% CI 0.64–1.43, $p = 0.83$). Kaplan–Meier curves for PFS on docetaxel are shown in Figure 2. Response rate to docetaxel was 61% and 54% for gDDR+ and gDDR– patients, respectively (Fisher's exact $p = 0.48$, Supplementary Table 4); this resulted in an odds ratio of response to docetaxel of 1.33 (95% CI 0.66–2.69; $p = 0.43$) for patients carrying gDDRm compared with gDDRm– patients.

3.4. *gDDRm and ARSIs (abiraterone, enzalutamide)*

PFS on first ARSI (either abiraterone or enzalutamide) for mCRPC was not significantly different for patients with or without gDDRm (HR 0.93, 95% CI 0.65–1.32, $p = 0.67$), with similar median PFS for gDDRm+ (8.3 mo) and gDDRm– (8.3 mo; Fig. 2). Patients with *BRCA2* mutations also had similar PFS to the overall population (HR 1.09, 95% CI 0.72–1.67, $p = 0.66$). Response rates to the first ARSI were 46% and 56% for gDDRm+ and gDDRm– patients, respectively (Fisher's exact $p = 0.28$, Supplementary Table 4), resulting in a nonsignificant trend towards a lower chance of response for gDDRm+ (odds ratio 0.65, 95% CI 0.32–1.32, $p = 0.23$).

3.5. *PARPi and platinum in patients with gDDRm*

In this cohort, 141 (36%) patients had received PARPi and/or platinum chemotherapy, including 28/60 (47%) gDDRm+ cases. We explored the potential interaction of these treatments and gDDRm on survival from castration resistance in this cohort.

Table 2 – Overall survival from castration resistance and progression-free survival to standard therapies

	aHR (MVA)	95% CI	*p* value
OS from castration resistance			
Any gDDRm+	0.93	0.63–1.37	0.72
Age at diagnosis (per 10 yr)	1.45	1.22–1.73	<0.001
Gleason 8–10	1.54	1.16–2.04	0.003
Metastatic disease	1.22	0.84–1.75	0.30
Radical treatment	1.50	1.03–2.18	0.03
	HR	95% CI	*p* value
PFS docetaxel			
Any gDDRm +	0.86	0.61–1.20	0.37
Only gBRCA2m+	0.96	0.64–1.43	0.83
PFS first line of ARS therapy			
Any gDDRm +	0.96	0.69–1.35	0.83
Only gBRCA2m+	1.10	0.72–1.67	0.67

aHR = adjusted hazard ratio; ARS = androgen receptor signal; CI = confidence interval; gDDRm = germline DNA damage repair gene mutation; MVA = multivariate analysis; PSA = prostate-specific antigen.
Results from a mixed-effect survival model (Weibull distribution) with random intercept per cohort.

There was no statistically significant impact from PARPi/platinum on OS for the overall population (aHR 0.97, 95% CI 0.73–1.31; $p = 0.88$). The hazard of death based on the presence of gDDR mutations once adjusted for exposure to

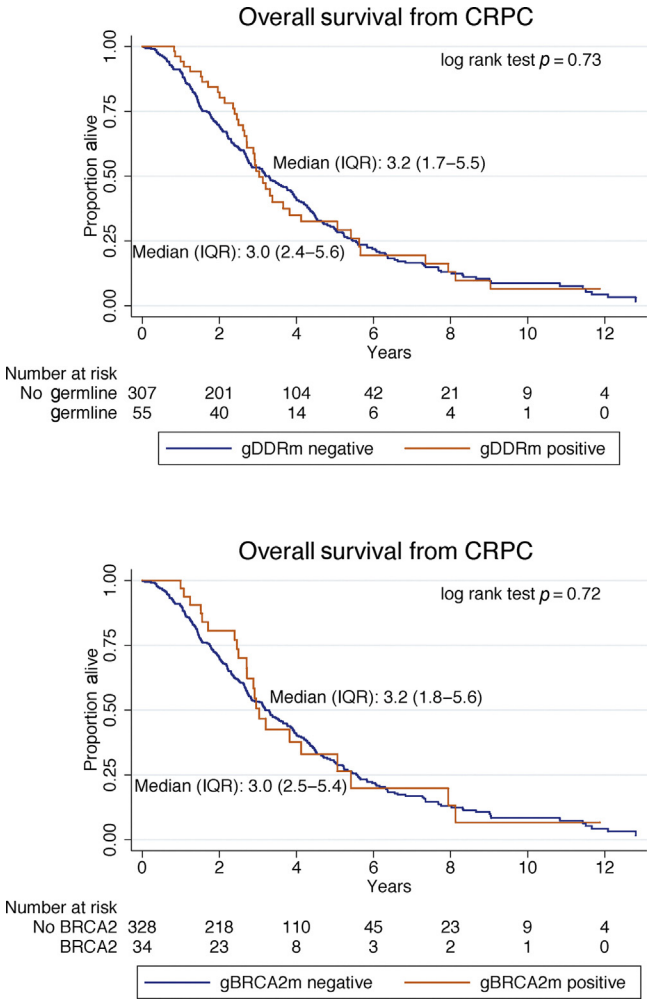


Fig. 1 – Kaplan–Meier curves for survival from date of castration resistance and from initial diagnosis based on the presence of gDDRm and specifically for gBRCA2m carriers. CRPC = castration-resistant prostate cancer; gDDRm = germline DNA damage repair gene mutation; IQR = interquartile range.

PARPi/platinum indicated no statistically significant difference in risk of death (aHR 1.23; 95% CI 0.73–2.07; $p = 0.44$).

An interaction test between gDDRm+ and PARPi/platinum therapy revealed an aHR of 0.59 (95% CI 0.28–1.25; $p = 0.17$). These data suggest that the association of gDDRm status and survival could have been impacted by the exposure to PARPi/platinum. Nevertheless, with this size of the gDDRm+ subgroup, no statistically significant differences were observed in this cohort and the null hypothesis could not be excluded. Survival curves illustrating the impact of PARPi/platinum by gDDRm status are shown in Figure 3.

4. Discussion

In this study, we retrospectively reviewed clinical outcome of lethal prostate cancer patients according to their gDDRm status [3]. Overall, we did not observe significant differences in response rate and PFS from docetaxel and ARSIs based on gDDRm status, suggesting that gDDRm+ carriers derive benefit from these therapies similarly to the overall population. These data are of major interest to the clinical community at this time in view of changes in NCCN guidelines in 2018 recommending germline testing for all men suffering from mPC [4].

Prior analyses interrogating this question have reported conflicting results. A recent retrospective study including 319 patients (22 gDDRm+, 16 being germline *BRCA2* mutation carriers) reported shorter OS and worse outcome from abiraterone/enzalutamide treatment, but not from docetaxel for mCRPC patients with gDDRm [13]. Preliminary results of a prospective clinical trial of abiraterone and the PARP inhibitor veliparib suggested conversely that prostate cancer patients with DDR defects (here including germline and somatic alterations) may actually be more likely to respond to abiraterone acetate therapy [16]. Differences in the baseline characteristics, genes included in each analysis, and distribution and prevalence of mutations between study populations may have accounted for these differences. The retrospective nature of ours and other studies is a significant limitation, and prospective validation is required in ongoing studies [15]. Data from breast cancer studies also suggest that patients with germline *BRCA1/2* mutations derive significant benefit from taxane-based chemotherapy [17].

A notable distinction of our patient cohort was the substantial proportion of patients treated with PARP inhibitors and/or platinum chemotherapy, which are not part of the standard of care for prostate cancer. This has to be taken into account when comparing the survival analysis in this study to others, since the introduction of these treatments may have impacted outcome. The use of such therapies should not, however, have impacted response data to the specific standard therapies presented here, since these were largely administered prior to the PARP inhibitor or platinum therapy. We observed a trend towards prolonged OS in gDDRm+ patients receiving PARPi/platinum. This interaction was not, however, statistically significant in this small gDDRm+ cohort, and may be a chance finding or have been impacted by other unrecognised confounding factors [7,8].

Another limitation of our study is the focus on germline, to the exclusion of somatic only, mutations [9,18,19]. It is estimated that 20–25% mPC have somatic inactivation of a DNA repair gene, but just less than half of these carry a germline mutation. Hence, it is likely that a substantial proportion of our cases in the gDDRm– group harboured somatic DDR defects and that some but not all the gDDRm+ cases would have had somatic inactivation of the second allele. Moreover, the lack of somatic DNA data for this cohort also prevented us from analysing the impact of other concurrent genomic events influencing prostate cancer progression, such as *AR*, *TP53*, or *RB1* aberrations. Studies assessing clinical outcome to specific therapies incorporating somatic genomic data are ongoing and will be fundamental to shape precision medicine strategies in mCRPC and complement ongoing clinical trials of DNA repair targeting agents in CRPC. These studies and prospective clinical trials will also need to control for other

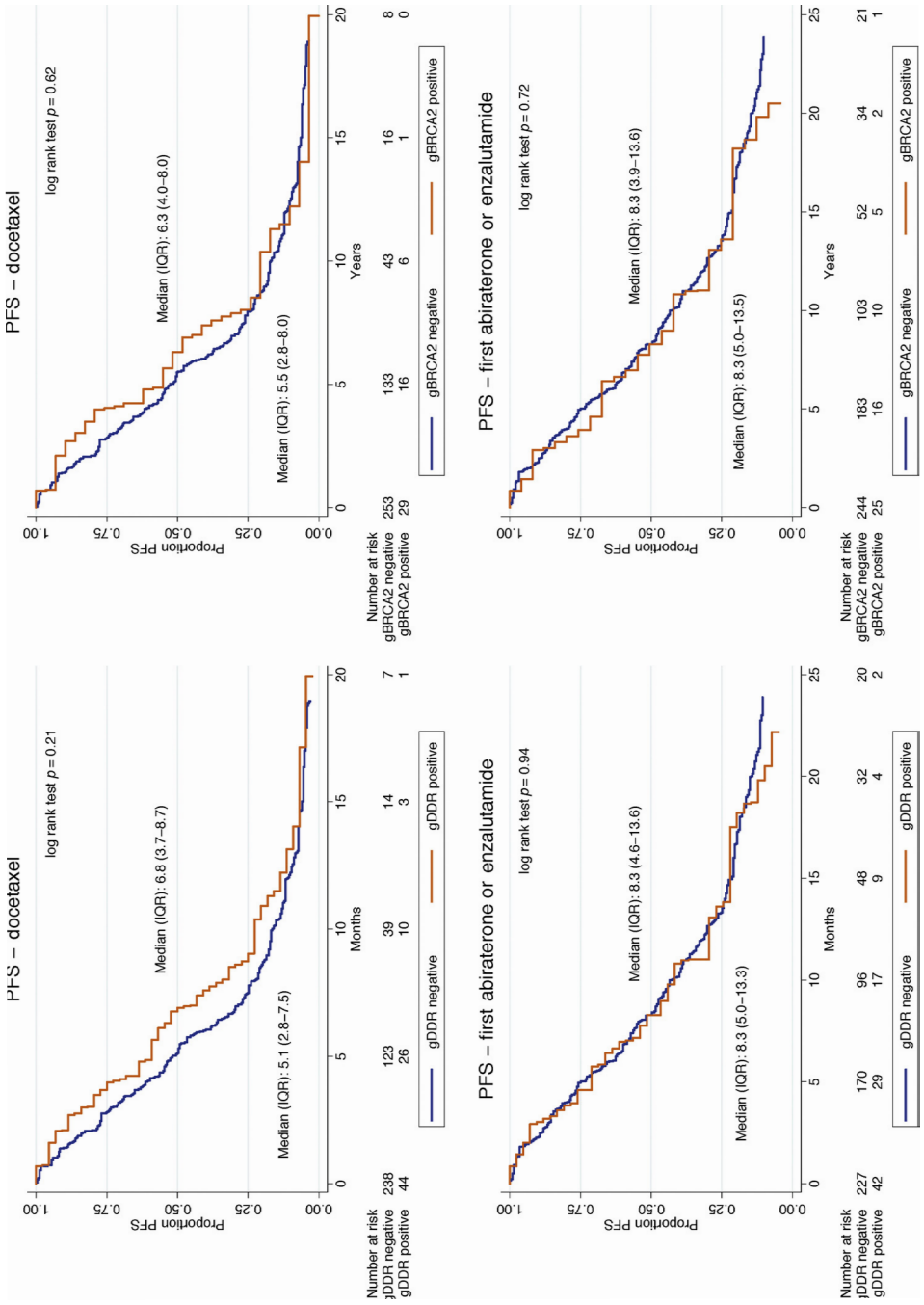


Fig. 2 – Kaplan–Meier curves for progression-free survival on docetaxel and first-line ARSI therapy based on the presence of any gDDRm. ARSI = androgen receptor signalling inhibitor; gDDRm = germline DNA damage repair gene mutation; IQR = interquartile range; PFS = progression-free survival.

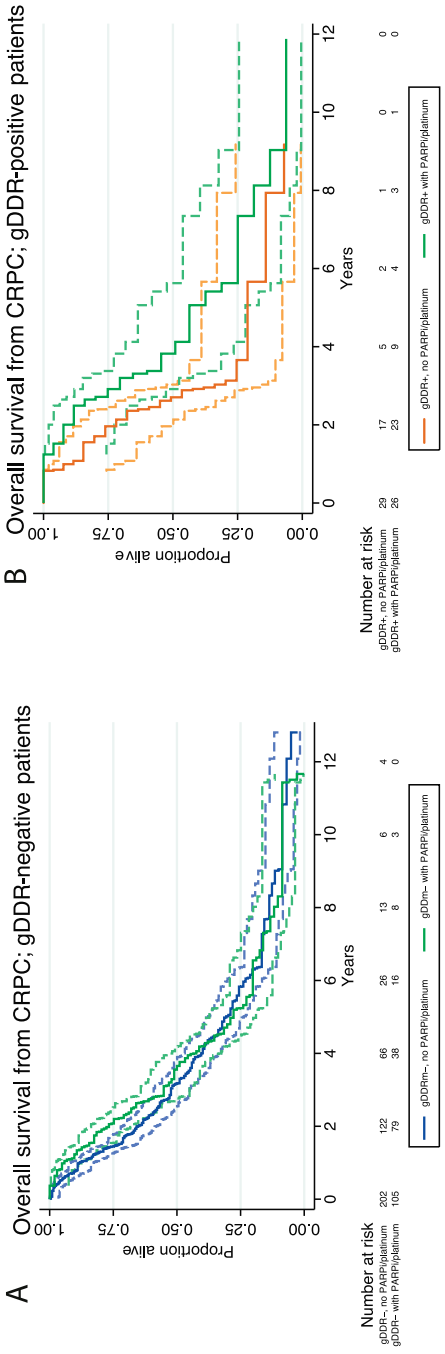


Fig. 3 – Kaplan–Meier curves depicting survival from detection of castration resistance, with patients grouped by exposure to PARP inhibitors and/or platinum therapy for (A) gDDRm+ or (B) gDDRm– metastatic castration-resistant prostate cancers. Dashed lines indicate the 95%CI limits. CI = confidence interval; CRPC = castration-resistant prostate cancer; gDDR = germline DNA damage repair; gDDRm = germline DNA damage repair gene mutation; IQR = interquartile range; PARPi = PARP inhibitor.

potential prognostic factors not assessed in this retrospective study.

5. Conclusions

The data presented here suggest that mPC patients with inherited mutations in DDR genes, including those with *BRCA2* mutations, can derive similar benefit from standard of care therapies in terms of both response rate and PFS. Based on the limitations described, we acknowledge that this study may not be sufficient to fully inform clinical decisions; in view of the discrepancies identified among different retrospective analyses, prospective studies are now needed evaluating the impact of germline DNA repair mutations in advanced prostate cancer, beyond their clear importance to prompt family cascade counselling. Nevertheless, our overall data indicate that detection of gDDRm should not preclude mPC patients from receiving taxanes, abiraterone, and enzalutamide as standards of care. Pivotal clinical trials of PARPi are ongoing for prostate cancer sufferers with germline and somatic DDRm, and may offer additional therapy options for this group of patients.

Author contributions: Johann S. de Bono had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Mateo, Cheng, Beltran, Rubin, Nelson, de Bono.
Acquisition of data: Mateo, Cheng, Beltran, Xu, Pritchard, Rescigno, Perez-Lopez, Sailer, Kolinsky, Balasopoulou, Bertan, Thorne, Sandhu.
Analysis and interpretation of data: Mateo, Cheng, Beltran, Dolling, Mossop.
Drafting of the manuscript: Mateo, Cheng, Beltran, Rubin, Nelson, de Bono.
Critical revision of the manuscript for important intellectual content: Mateo, Cheng, Beltran, Dolling, Xu, Pritchard, Mossop, Rescigno, Perez-Lopez, Sailer, Kolinsky, Balasopoulou, Bertan, Carreira, Montgomery, Nanus, Tagawa, Thorne, Sandhu, Rubin, Nelson, de Bono.
Statistical analysis: Dolling, Mossop.
Obtaining funding: Rubin, Nelson, de Bono.
Administrative, technical, or material support: Balasopoulou, Thorne.
Supervision: Sandhu, Rubin, Nelson, de Bono.
Other: Patient recruitment: Mateo, Cheng, Beltran, Rescigno, Kolinsky, Nanus, Montgomery, Tagawa.

Financial disclosures: Johann S. de Bono certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: J. Mateo, D. Dolling, H. Mossop, P. Rescigno, R. Perez-Lopez, M. Kolinsy, A. Balasopoulou, C. Bertan, S. Carreira, and J. de Bono are employees of the Institute of Cancer Research, which is a joint applicant in patents involving PARP inhibitors and receive royalties from the development of abiraterone. S.T. Tagawa declares honoraria from Sanofi and Janssen. M.A. Rubin is a cofounder of Thucydx LLC. J. de Bono has served as an advisor for AZ, Janssen, Pfizer, Qiagen, Sanofi-Aventis.

Funding/Support and role of the sponsor: None.

Acknowledgements: This work was supported by a Stand Up To Cancer-Prostate Cancer Foundation Prostate Dream Team Translational Cancer

Research Grant. Stand Up To Cancer is a program of the Entertainment Industry Foundation administered by the American Association for Cancer Research (SU2C-AACR-DT0712). We also acknowledge support from Movember and Prostate Cancer UK, and from the KConFab consortium (Kathleen Cuningham Foundation Consortium for research into familial breast cancer; Australia) for providing data for this report. J. Mateo, H. Cheng, H. Beltran, and C. Pritchard were supported by Prostate Cancer Foundation Young Investigator Awards. We also acknowledge funding support from NIH/NCI (P50CA097186), the Institute for Prostate Cancer Research (Seattle, WA, USA), a Medical Research Council-Prostate Cancer UK fellowship (J. Mateo), an Experimental Cancer Medical Centre grant, and a Biomedical Research Centre grant to the ICR/Royal Marsden. S. Sandhu was supported by a Prostate Cancer Foundation of Australia Young Investigator Award.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.01.010.

References

[1] Kote-Jarai Z, Leongamornlert D, Saunders E, et al. BRCA2 is a moderate penetrance gene contributing to young-onset prostate cancer: implications for genetic testing in prostate cancer patients. Br J Cancer 2011;105:1230–4.

[2] Eeles R, Goh C, Castro E, et al. The genetic epidemiology of prostate cancer and its clinical implications. Nat Rev Urol 2014;11:18–31.

[3] Pritchard CC, Mateo J, Walsh MF, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med 2016;375:443–53.

[4] National Comprehensive Cancer Network. Genetic/familial high-risk assessment: breast and ovarian. 2018 https://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf

[5] Fong PCP, Boss DDS, Yap TA, et al. Inhibition of poly (ADP-ribose) polymerase in tumors from BRCA mutation carriers. N Engl J Med 2009;361:123–34.

[6] Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med 2012;366:1382–92.

[7] Mateo J, Carreira S, Sandhu S, et al. DNA-repair defects and olaparib in metastatic prostate cancer. N Engl J Med 2015;373:1697–708.

[8] Cheng HH, Pritchard CC, Boyd T, Nelson PS, Montgomery B. Biallelic inactivation of BRCA2 in platinum-sensitive metastatic castration-resistant prostate cancer. Eur Urol 2016;69:992–5.

[9] Robinson D, Van Allen EM, Wu Y-M, et al. Integrative clinical genomics of advanced prostate cancer. Cell 2015;161:1215–28. http://dx.doi.org/10.1016/j.cell.2015.05.001.

[10] Abeshouse A, Ahn J, Akbani R, et al. The molecular taxonomy of primary prostate cancer. Cell 2015;163:1011–25.

[11] Castro E, Goh C, Olmos D, et al. Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. J Clin Oncol 2013;31:1748–57.

[12] Castro E, Goh C, Leongamornlert D, et al. Effect of BRCA mutations on metastatic relapse and cause-specific survival after radical treatment for localised prostate cancer. Eur Urol 2015;68:186–93.

[13] Annala M, Struss WJ, Warner EW, et al. Treatment outcomes and tumor loss of heterozygosity in germline DNA repair–deficient prostate cancer. Eur Urol 2017;72:34–42.

[14] Gallagher DJ, Cronin AM, Milowsky MI, et al. Germline BRCA mutation does not prevent response to taxane-based therapy for the treatment of castration-resistant prostate cancer. BJU Int 2012;109:713–9.

[15] Castro E, Romero-Laorden N, Piulats J, et al. PROREPAIR-B: a prospective cohort study of DNA repair defects in metastatic castration resistant prostate cancer. Ann Oncol 2017;28(Suppl 5):LBA32.

[16] Hussain M, Daignault S, Twardowski P, et al. Co-targeting androgen receptor (AR) and DNA repair: a randomized ETS gene fusion-stratified trial of abiraterone + prednisone (Abi) +/– the PARP1 inhibitor veliparib for metastatic castration-resistant prostate cancer (mCRPC) patients (pts) (NCI9012). J Clin Oncol 2016;34 (Suppl):5010.

[17] Hahnen E, Lederer B, Hauke J, et al. Germline mutation status, pathological complete response, and disease-free survival in triple-negative breast cancer. JAMA Oncol 2017;3:1378.

[18] Beltran H, Yelensky R, Frampton GM, et al. Targeted next-generation sequencing of advanced prostate cancer identifies potential therapeutic targets and disease heterogeneity. Eur Urol 2013;63:920–6.

[19] Abida W, Armenia J, Gopalan A, Brennan R. Prospective genomic profiling of prostate cancer across disease states reveals germline and somatic alterations that may affect clinical decision making. JCO Precis Oncol 2017. http://dx.doi.org/10.1200/PO.17.00029, Epub 2017 May 31.

ELSEVIER

Urologic Oncology: Seminars and Original Investigations 36 (2018) 385–388

UROLOGIC ONCOLOGY

Seminars article

The resounding effect of DNA repair deficiency in prostate cancer

Heather H. Cheng, M.D., Ph.D.[a,b,*]

[a] *Division of Medical Oncology, University of Washington, Seattle, WA*
[b] *Division of Clinical Research, Fred Hutchinson Cancer Research Center, Seattle, WA*

Received 10 September 2017; received in revised form 17 February 2018; accepted 21 February 2018

Abstract

An estimated one-fifth or more of metastatic castration-resistant prostate cancer (mCRPC) harbor defects in genes involved in DNA repair pathway (e.g., *BRCA2, BRCA1*, and others). Early evidence suggests these alterations may be predictive of therapeutic response to PARP inhibitors and platinum chemotherapy, thought to reflect principles of synthetic lethality and are currently being investigated in an increasing number of prospective clinical trials. Other studies have examined these alterations as prognostic biomarkers and in association with response to currently available treatments. A smaller fraction of men (5%–10%) with mCRPC have evidence of microsatellite instability and defects in the DNA mismatch repair pathway, which may predict therapeutic response to immune checkpoint inhibitors. Loss of function of these 2 critical DNA repair pathways serves as new candidate predictive biomarkers for treatment strategies that represent net gains in the treatment toolbox for prostate cancer. Additionally, more than one-tenth of men with mCRPC carry genetic alterations of DNA repair in their germline DNA, which may indicate high- to moderate-penetrance heritable cancer risk and have important implications for family members. Cascade genetic testing of family can, in some cases, direct modified strategies for screening and prevention of multiple cancers. Further study in each of these arenas is ongoing, although the potential for resounding effect is clear.

Keywords: Prostate Cancer; DNA repair; Biomarker; PARP inhibitor; Germline

New precision targets

The prostate cancer research field has recently witnessed a series of important discoveries revolving around genes critical to DNA repair and is beginning to harness the potential of these findings in earnest. In 2015, the Cancer Genome Atlas Research Network reported findings from 333 primary prostate cancers and the identification of 19% of primary tumors with mutations in DNA repair genes, including 3% in the homologous recombination repair gene, *BRCA2* [1]. In the same year, the International SU2C/PCF/AACR Prostate Cancer Dream Team applied exome sequencing to 150 metastatic biopsies and found approximately 20% of metastatic prostate cancers with alterations in genes critical to DNA repair, notably involving homologous recombination repair (*BRCA2, ATM*, and *BRCA1*) as well as mismatch repair (*MLH1* and *MSH2*) [2]. Other studies have validated the high prevalence of DNA repair alterations in metastatic castration-resistant prostate cancers (mCRPC) [3,4].

Deficiencies in specific DNA repair pathways have been characterized in other cancers where treatments exploit these deficiencies using principles of synthetic lethality (Fig). The basic rationale is that cancers with specific inactivation of one of a number of DNA repair pathways will render the cancer more reliant on the remaining intact repair pathways. However, drugs such as PARP inhibitors can inactivate one of the remaining DNA repair pathways, which is lethal in cancer cells (where there is insufficient DNA repair capacity to compensate), while being relatively less toxic in noncancerous cells (where there is sufficient remaining intact DNA repair capacity to compensate). These discoveries are major strides in the field, as they represent molecular subsets that may benefit from precision therapies and thus are promising candidate predictive biomarkers.

Homologous recombination deficiency

Following on the discovery that a significant proportion of mCRPC harbors defects in DNA repair was early,

H.C. receives research funding from the National Cancer Institute of the National Institutes of Health, United States; Institute for Prostate Cancer Research; the Pacific Northwest Prostate Cancer SPORE (CA097186); Prostate Cancer Foundation, United States; and NIH/NCI Cancer Center Support (Grant P30 CA015704), Janssen, Inovio, Celgene, and Sanofi.

* Corresponding author. Tel.: +1-206-606-7595.
E-mail address: hhcheng@uw.edu

https://doi.org/10.1016/j.urolonc.2018.02.014
1078-1439/

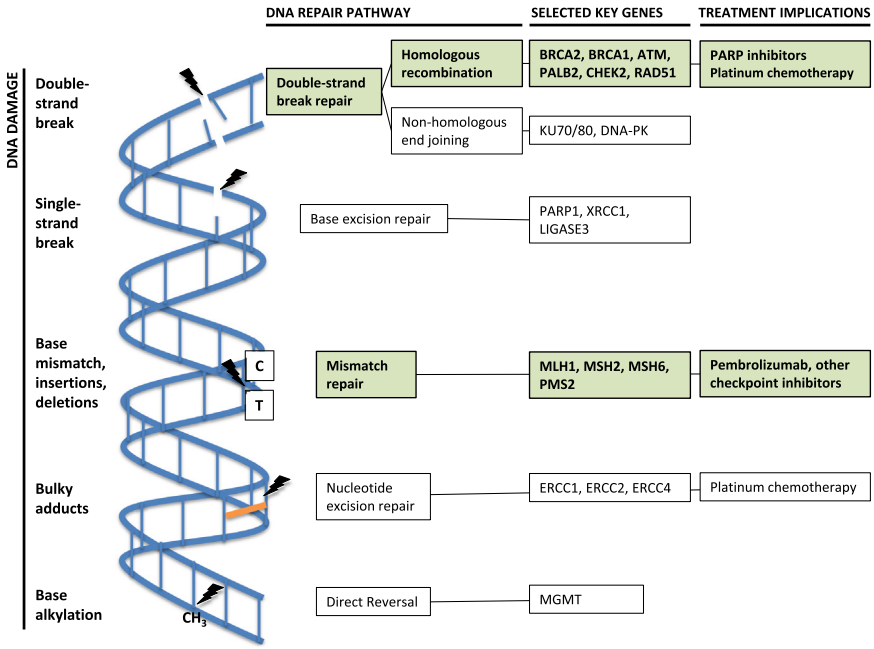


Fig. Schematic overview of major types of DNA damage, along with the corresponding DNA damage repair mechanisms, key genetic drivers, and treatment implications. Boxes denote components with particular new relevance to advanced prostate cancer. (Color version of figure is available online.)

biologically plausible evidence of clear therapeutic consequence–that not only PARP inhibitors but also platinum chemotherapy may have particular efficacy in prostate cancer with homologous recombination repair deficiency [5–7]: the TOPARP-A study showed that 14/16 (88%) of heavily pretreated patients with mCRPC who had defects in DNA repair genes had a response to the poly ADP ribosylase (PARP) inhibitor olaparib [5]. There are now a substantial number of clinical trials underway investigating PARP inhibitors in mCRPC with evidence of homologous DNA repair inactivation (Table).

In addition, several reports show notably improved response to platinum chemotherapy in patients with metastatic prostate cancer containing inactivating mutations of *BRCA2,* germline and somatic-only. In our case series from the University of Washington and Fred Hutchinson Cancer Center, 3 heavily pretreated patients observed to have exceptional responses to addition of carboplatin chemotherapy (up to 30 mo of PSA-progression-free survival) underwent tumor next generation sequencing and all were found to have evidence of biallelic inactivation of *BRCA2.* Notably, 2 patients had underlying germline *BRCA2* pathogenic mutations [6]. In another single-institutional study of 141 men treated with at least 2 cycles of carboplatin and docetaxel for mCRPC, pathogenic germline *BRCA2* variants were observed in 8/141 men (5.7%; 95% CI, 2.5%–10.9%). Six of 8 *BRCA2* mutation carriers (75%) experienced PSA declines >50% within 12 weeks, compared with 23 of 133 noncarriers (17%; absolute difference, 58%; 95% CI, 27%–88%; $P < 0.001$) [8]. There are also prospective clinical trials underway examining treatment with platinum chemotherapy for patients with mCRPC (Table).

Mismatch repair deficiency and microsatellite instability

In May of 2017, the U.S. Food and Drug Administration granted approval to pembrolizumab for patients with unresectable or metastatic solid tumors with progression or no alternative treatments that have microsatellite instability (MSI) or mismatch repair deficiency, agnostic of tissue/site indication—in this regard, the first FDA-approval of its kind. A small subset of advanced prostate cancers have been reported to have complex *MSH2* or *MSH6* structural rearrangements resulting in hypermutation [2,8]. Preliminary findings from a combination study adding pembrolizumab at time of resistance to enzalutamide revealed one exceptional responder with evidence of tumor MSI (www.clinicaltrials.gov; NCT02312557) [9]. Thus, MSI/mismatch repair deficient suggests that immune checkpoint inhibition may be another precision-guided treatment avenue for a subset of men with advanced prostate cancer. It remains to be determined whether the combination of enzalutamide and pembrolizumab exerts a different effect on prostate cancer compared to monotherapy with pembrolizumab alone, and whether there are therapeutic differences between different timing and sequences of combinations. Other novel approaches include combination of immune checkpoint inhibitors and PARPi, with the goal of forcing errors in tumor replication and potentially rendering greater tumor antigenicity and visibility to the immune system.

Therapeutic opportunities

These findings have proven exhilarating to the prostate cancer field that has eagerly awaited delivery on the

Table
Selected trials in prostate cancers related to DNA repair

Phase	Title	Disease state		Clinicaltrials.gov
III	Study of olaparib (Lynparza) vs. enzalutamide or abiraterone acetate in men with metastatic castration-resistant prostate cancer (PROfound Study)	mCRPC	PROFOUND	NCT02987543
III	A study of rucaparib verses physician's choice of therapy in patients with metastatic castration-resistant prostate cancer and homologous recombination gene deficiency (TRITON3)	mCRPC	TRITON3	NCT02975934
II	A phase 2 efficacy and safety study of niraparib in men with metastatic castration-resistant prostate cancer and DNA-repair anomalies	mCRPC	GALAHAD	NCT02854436
II	A multicenter, open-label phase 2 study of rucaparib in patients with metastatic castration-resistant prostate cancer associated with homologous recombination deficiency	mCRPC	TRITON2	NCT02952534
II	Response rate study of talazoparib in men with DNA repair defects and metastatic castration-resistant prostate cancer who previously received taxane-based chemotherapy and progressed on at least 1 novel hormonal agent (enzalutamide or abiraterone acetate/prednisone)	mCRPC		NCT03148795
II	Olaparib in men with high-risk biochemically recurrent prostate cancer following radical prostatectomy, with integrated biomarker analysis	BCR		NCT03047135
II	Abiraterone/prednisone, olaparib, or abiraterone/prednisone + olaparib in patients with metastatic castration-resistant prostate cancer with DNA repair defects	mCRPC	BRCAaway	NCT03012321
I	A safety and pharmacokinetics study of niraparib plus an androgen receptor-targeted therapy in men with metastatic castration-resistant prostate cancer (BEDIVERE)	mCRPC	BEDIVERE	NCT02924766
Pilot	Docetaxel and carboplatin in treating patients with metastatic, hormone resistant prostate cancer containing inactivated genes in the BRCA 1/2 pathway	mCRPC	ABCD	NCT02598895
II	The BARCODE 2 study - the use of genetic profiling to guide prostate cancer treatment (BARCODE2)	mCRPC	BARCODE-2	NCT02955082
II	Docetaxel and carboplatin for patients with mCRPC and DNA-repair deficiencies	mCRPC	V-ABCD	NCT02985021
II	Pembrolizumab in treating patients with metastatic castration-resistant prostate cancer previously treated with enzalutamide	mCRPC		NCT02312557
II	Study of pembrolizumab (MK-3475) in participants with metastatic castration-resistant prostate cancer	mCRPC	KEYNOTE-199	NCT02787005
Ib/II	Study of pembrolizumab (MK-3475) combination therapies in metastatic castration-resistant prostate cancer	mCRPC	KEYNOTE-365	NCT02861573

promise of precision oncology: we now have new candidate predictive biomarkers (homologous recombination deficiency, mismatch repair deficiency/MSI) for new treatments and a clear view of net gains in the therapeutic toolbox. Currently, clinical trials incorporating these targeted agents alone and in combination with other agents for prostate cancer are ongoing and in development (Table, www.clinicaltrials.gov).

Mechanisms of resistance

Synthetic lethality in homologous recombination deficient cancers has been extensively explored in ovarian and breast cancers, and some mechanisms of resistance to PARPi and platinum have been described, including reversion mutations (i.e., secondary mutations restoring open reading frames) [10–13]. Indeed, several reports in prostate cancer patients have already described reversion mutations of mutations in *BRCA2* and *PALB2* in the plasma ctDNA as a mechanism of resistance to PARPi and platinum [14,15] (Cheng et al. JCO PO, in press; Carneiro et al., JCO PO, in press). These reports are sobering in that, as with AR-targeting agents, the drive to resistance is a persistent force though the ability to detect resistant clones early may offer opportunities to triage to clinical trials to prevent development of resistance, such as through combination approaches.

Germline implications

There is little question that the new relevance of DNA repair deficiency in advanced prostate cancer has led to an abundance of new opportunities and therapeutic directions. In 2016, a dedicated germline study of nearly 700 men with metastatic prostate cancer found 11.8% harboring pathogenic germline mutations associated with high- to moderate-penetrance cancer predisposition, including *BRCA2*, *BRCA1* along with a number of other less common DNA repair genes newly associated with prostate cancer [16]. This discovery that approximately half of these treatment-actionable genetic alterations lie in the germline DNA (and are therefore heritable) may be an equally ripe opportunity for the field.

We have long recognized that family history of prostate cancer is a major risk factor for developing prostate cancer. The genetic risk is composed of a combination of common risk and modifying alleles as well as, in some men, relatively rare mutations in moderate-high penetrance cancer risk genes such as *BRCA2*. Both are important, but knowledge of moderate-high penetrance genes carries management recommendations for carriers who may be at increased risk of multiple cancers (NCCN clinical practice guidelines for genetic/familial high-risk assessment: breast and ovarian, genetic/familial high-risk assessment: colorectal.).

A number of groups have now demonstrated the clear limitations of prior criteria (largely family history of cancer)

for identification of men with prostate cancer and single-gene, high- to moderate-penetrance cancer predisposition (*BRCA2, BRCA1*, etc.) [16,17]. Moreover, germline carriers of *BRCA2* pathogenic mutations have worse prostate-cancer specific outcomes [18–20]. Germline mutation carriers who are at risk for prostate cancer may be candidates for modified cancer screening [21,22], and those with localized prostate cancer might be considered for clinical trials of treatment intensification to improve outcomes.

The identification of carriers of rare germline pathogenic mutation carriers among those diagnosed with metastatic prostate cancer can also facilitate cascade genetic testing (genetic testing of at-risk family members where each first degree relative has a 50% chance of inheriting the same risk variant), and with it more informed and tailored cancer risk management in these relatives. Alternate approaches are being explored in universal screening of colon and endometrial cancer patients for Lynch Syndrome [23], and similarly in hereditary breast and ovarian cancer syndrome [24,25].

Concerted efforts to determine best approaches to implementation of cascade genetic testing of family members are underway, and more work is needed to understand newer, less characterized variants and genes with respect to clarification of prostate cancer risk, consequent measures for early detection and prevention of not only prostate, but potentially also breast, ovarian, colon, and endometrial cancers, among others. New dedicated clinics and clinical trials are opening to address delivery, characterize risk, and improve management approaches.

Summary

Many new investigative areas and opportunity have arisen from recent discoveries around DNA repair in advanced prostate cancer: precision therapy opportunities (PARPi, platinum, immune-checkpoint inhibitors, and new combination approaches), liquid tumor biopsies in the form of circulating tumor cells and cell-free circulating tumor DNA, research and clinical considerations around germline pathogenic variants in DNA repair genes that could translate to improved management of the next generation (cancer risk management in family members). The full extent of affect will not be realized for a long time to come, but will undoubtedly lead to better outcomes for prostate cancer patients and their families.

References

[1] Cancer Genome Atlas Research N: The molecular taxonomy of primary prostate cancer. Cell 2015;163:1011–25.
[2] Robinson D, Van Allen EM, Wu YM, et al. Integrative clinical genomics of advanced prostate cancer. Cell 2015;161:1215–28.
[3] Beltran H, Eng K, Mosquera JM, et al. Whole-exome sequencing of metastatic cancer and biomarkers of treatment response. J Am Med Assoc Oncol 2015;1:466–74.
[4] Abida W, Armenia J, Gopalan A, et al. Prospective genomic profiling of prostate cancer across disease states reveals germline and somatic alterations that may affect clinical decision making. JCO Precis Oncol 2017;2017.
[5] Mateo J, Carreira S, Sandhu S, et al. DNA-repair defects and olaparib in metastatic prostate cancer. N Engl J Med 2015;373:1697–708.
[6] Cheng HH, Pritchard CC, Boyd T, et al. Biallelic inactivation of BRCA2 in platinum-sensitive metastatic castration-resistant prostate cancer. Eur Urol 2016;69:992–5.
[7] Pomerantz MM, Spisak S, Jia L, et al. The association between germline BRCA2 variants and sensitivity to platinum-based chemotherapy among men with metastatic prostate cancer. Cancer 2017;123:3532–9.
[8] Pritchard CC, Morrissey C, Kumar A, et al. Complex MSH2 and MSH6 mutations in hypermutated microsatellite unstable advanced prostate cancer. Nat Commun 2014;5:4988.
[9] Graff JN, Alumkal JJ, Drake CG, et al. Early evidence of anti-PD-1 activity in enzalutamide-resistant prostate cancer. Oncotarget 2016;7:52810–7.
[10] Swisher EM, Sakai W, Karlan BY, et al. Secondary BRCA1 mutations in BRCA1-mutated ovarian carcinomas with platinum resistance. Cancer Res 2008;68:2581–6.
[11] Sakai W, Swisher EM, Karlan BY, et al. Secondary mutations as a mechanism of cisplatin resistance in BRCA2-mutated cancers. Nature 2008;451:1116–20.
[12] Kondrashova O, Nguyen M, Shield-Artin K, et al. Secondary somatic mutations restoring RAD51C and RAD51D associated with acquired resistance to the PARP inhibitor rucaparib in high-grade ovarian carcinoma. Cancer Discov 2017;7:984–98.
[13] Christie EL, Fereday S, Doig K, et al. Reversion of BRCA1/2 germline mutations detected in circulating tumor DNA from patients with high-grade serous ovarian cancer. J Clin Oncol 2017;35:1274–80.
[14] Annala M, Struss WJ, Warner EW, et al. Treatment outcomes and tumor loss of heterozygosity in germline DNA repair-deficient prostate cancer. Eur Urol 2017;72:34–42.
[15] Goodall J, Mateo J, Yuan W, et al. Circulating free DNA to guide prostate cancer treatment with PARP inhibition. Cancer Discov 2017.
[16] Pritchard CC, Mateo J, Walsh MF, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med 2016;375:443–53.
[17] Pilie PG, Johnson AM, Hanson KL, et al. Germline genetic variants in men with prostate cancer and one or more additional cancers. Cancer 2017;123:3925–32.
[18] Castro E, Goh C, Olmos D, et al. Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. J Clin Oncol 2013;31:1748–57.
[19] Castro E, Goh C, Leongamornlert D, et al. Effect of BRCA mutations on metastatic relapse and cause-specific survival after radical treatment for localised prostate cancer. Eur Urol 2015;68:186–93.
[20] Na R, Zheng SL, Han M, et al. Germline mutations in ATM and BRCA1/2 distinguish risk for lethal and indolent prostate cancer and are associated with early age at death. Eur Urol 2017;71:740–7.
[21] Bancroft EK, Page EC, Castro E, et al. Targeted prostate cancer screening in BRCA1 and BRCA2 mutation carriers: results from the initial screening round of the IMPACT study. Eur Urol 2014;66:489–99.
[22] Cheng HH, Pritchard CC, Montgomery B, et al. Prostate cancer screening in a new era of genetics. Clin Genitourin Cancer 2017;15:625–8.
[23] Hampel H. Genetic counseling and cascade genetic testing in Lynch syndrome. Fam Cancer 2016;15:423–7.
[24] George A, Riddell D, Seal S, et al. Implementing rapid, robust, cost-effective, patient-centred, routine genetic testing in ovarian cancer patients. Sci Rep 2016;6:29506.
[25] Kwon JS, Daniels MS, Sun CC, et al. Preventing future cancers by testing women with ovarian cancer for BRCA mutations. J Clin Oncol 2010;28:675–82.

Metastatic Castration-Sensitive Prostate Cancer: Optimizing Patient Selection and Treatment

Andrew W. Hahn, MD, Celestia S. Higano, MD, Mary-Ellen Taplin, MD, Charles J. Ryan, MD, and Neeraj Agarwal, MD

OVERVIEW

The treatment landscape for metastatic castration-sensitive prostate cancer (mCSPC) has rapidly evolved over the past 5 years. Although androgen-deprivation therapy (ADT) is still the backbone of treatment, the addition of docetaxel or abiraterone acetate has improved outcomes for patients with mCSPC and become standard of care. With multiple treatment options available for patients with mCSPC, treatment selection to optimize patient outcomes has become increasingly difficult. Here, we review the clinical trials involving ADT plus docetaxel or abiraterone and provide clinicians with guidelines for treatment. Although surgery and/or radiation are standard of care for localized, intermediate- and high-risk prostate cancer, these treatments are not routinely used as part of initial treatment plans for patients with de novo mCSPC. Recent clinical data are challenging that dogma, and we review the literature on the addition of surgery and radiation to systemic therapy for mCSPC. Finally, the standard of care for oligometastatic prostate cancer (a subset of mCSPC with limited metastases) has not been established compared with that for some other cancers. We discuss the recent studies on metastasis-directed therapy for treatment of oligometastatic prostate cancer.

Prostate cancer accounts for one in every five cancer diagnoses, making it the most common cancer in men, and metastatic prostate cancer is the second most common cause of cancer-related deaths in men in the United States.[1] The incidence of prostate cancer began to decline in 2000, and it has more rapidly declined since the U.S. Preventive Services Task Force changed its recommendations for prostate-specific antigen (PSA) screening in 2008 and 2011.[1,2] However, over the same period in the United States, the incidence of metastatic prostate cancer is increasing, with at least one study showing a 72% higher incidence of mCSPC cases in 2013 than in 2004.[3,4] Whether the increase in mCSPC is specifically related to changes in screening recommendations is unknown; however, this increase is concerning because mCSPC is generally considered to be incurable. Although localized prostate cancer has a 5-year survival rate of 100%, mCSPC has a 5-year survival rate of 29.8%.[5]

The treatment of mCSPC has significantly changed over the past 5 years. The backbone of treatment of mCSPC is ADT to deprive prostate cancer cells of growth-stimulating androgens.[6] In 2013, the results of a phase III study of continuous versus intermittent ADT (SWOG9346) questioned the role of intermittent ADT. Further incremental progress in the outcome of patients with mCSPC came from the addition of novel agents, docetaxel or abiraterone, to ADT for more aggressive up-front treatment of metastatic prostate cancer. Since 2015, two clinical trials, CHAARTED and STAMPEDE arm C, demonstrated that up-front docetaxel plus ADT improves overall survival (OS) in patients with mCSPC.[7,8] Then, in 2017, two clinical trials, LATITUDE and STAMPEDE arm G, showed that up-front abiraterone plus prednisone plus ADT improves OS to a similar degree as docetaxel plus ADT did.[9,10] These clinical trials improved the prognosis for patients with mCSPC for the first time; however, they also present clinicians with a challenge to optimize treatment selection for individual patients among ADT alone, ADT plus docetaxel, and ADT plus abiraterone. To date, no head-to-head comparisons of ADT plus docetaxel versus ADT plus abiraterone are formally published. Additionally, a logical clinical question to ask is,what is the value of adding both docetaxel and abiraterone to standard castration therapy? Currently, there are no data to support this approach.

We begin by discussing the agents available for ADT and efficacy of different dosing regimens. We then more closely analyze the evolving treatment paradigm for mCSPC, including ADT plus docetaxel, ADT plus abiraterone, and novel combinations currently being investigated. After reviewing

From the Division of Oncology, University of Utah/Huntsman Cancer Institute, Salt Lake City, UT; Division of Oncology, University of Washington/Fred Hutchinson Cancer Research Center, Seattle, WA; Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA; Division of Hematology/Oncology, University of California-San Francisco, Helen Diller Comprehensive Cancer Center, San Francisco, CA.

Disclosures of potential conflicts of interest provided by the authors are available with the online article at asco.org/edbook.

Corresponding Author: Neeraj Agarwal, MD, Huntsman Cancer Institute, University of Utah, 2000 Circle of Hope Dr., Suite 5726, Salt Lake City, UT 84112; email: neeraj.agarwal@hci.utah.edu.

the available data, we discuss considerations for selection of the optimal treatment regimen for individual patients with mCSPC. Finally, we review the role for addition of surgery and/or radiotherapy to systemic therapy in de novo mCSPC and multimodality therapy for oligometastatic prostate cancer.

EVOLVING TREATMENT PARADIGM OF METASTATIC CASTRATION-SENSITIVE PROSTATE CANCER

Androgen-Deprivation Therapy

In mCSPC, prostate cancer cells need high levels of androgens to drive cancer growth.[11] Accordingly, approximately 90% of patients with mCSPC will respond to initial treatment with ADT.[12] ADT for mCSPC works by decreasing testicular production of androgens.[13] There are multiple mechanisms of action to block testicular production of androgens, including orchiectomy, luteinizing hormone–releasing hormone (LHRH) agonists to prevent luteinizing hormone secretion, and LHRH antagonists to decrease luteinizing hormone secretion. Two LHRH agonists, leuprolide and goserelin, are approved in the United States, whereas degarelix is the only LHRH antagonist approved there. The first-generation antiandrogens flutamide, nilutamide, and bicalutamide are not recommended as monotherapy for mCSPC; however, they are frequently used when LHRH agonists are initiated to prevent testosterone flare.[14] Until 2015, combined androgen blockade with an LHRH agonist and a first-generation antiandrogen was commonly used to treat mCSPC. Combined androgen blockade with first-generation antiandrogens can be considered, but data supporting the benefits are small. Furthermore, second-generation androgen receptor (AR) antagonists or androgen synthesis inhibitors may negate the observed benefits (Fig. 1).

Recent investigations have studied the optimal dosing schedule of ADT to balance efficacy with patient quality of life. In a phase III clinical trial of 3,040 men with newly diagnosed metastatic hormone-sensitive prostate cancer (mHSPC), SWOG studied whether intermittent ADT is noninferior to continuous ADT.[15] All patients were initially treated with 7 months of continuous ADT then randomly assigned to continuous or intermittent ADT if they had an ongoing PSA response. The coprimary endpoints for SWOG 9346 were noninferiority of intermittent ADT with respect to OS and quality of life 3 months after randomization. Unsurprisingly, intermittent ADT was associated with improved quality of life 3 months after randomization but not later because of the variable period of time "off therapy." However, intermittent ADT was not found to be noninferior to continuous ADT with respect to OS (5.8 years vs. 5.1 years; hazard ratio [HR], 1.10; 95% CI, 0.99–1.23) but rather the result was inconclusive. However, SWOG 9346 raised concerns about intermittent ADT, thus perpetuating continuous ADT as the favored therapy for mCSPC.

Analyses of several clinical trials have suggested that more aggressive up-front treatment could translate to improved outcomes for patients with mCSPC. In a subgroup analysis of 1,345 patients from SWOG 9346, lower PSA values after 7 months of continuous ADT were predictive of improved median OS.[16] Specifically, the 383 (25%) patients with a PSA greater than 4 ng/mL had a median OS of 13 months, whereas the 602 (45%) patients with a PSA less than 0.2 ng/mL had a median OS of 75 months. A follow-up analysis from the PR-7 trial, in men with biochemically recurrent prostate cancer, found that lower testosterone levels were predictive of improved cancer-specific survival and time to castration-resistant prostate cancer (CRPC).[17] These studies suggested that deeper androgen blockade could improve clinical outcomes for patients with mCSPC.[18]

PRACTICAL APPLICATIONS

- **ADT plus docetaxel for six cycles is considered a standard of care for high-volume mCSPC based on the CHAARTED, STAMPEDE arm C, and GETUG-AFU 15 clinical trials.**
- **ADT plus abiraterone acetate continued until disease progression is considered a standard of care for all patients with mCSPC based on the LATITUDE and STAMPEDE arm G clinical trials.**
- **Predictive biomarkers are needed to select patients for ADT plus docetaxel versus ADT plus abiraterone. Until those are identified, ADT plus docetaxel may be considered for patients with mCSPC who have more than four metastases, have a good performance status, desire shorter total treatment time, or have concerns for prescription drug costs; ADT plus abiraterone acetate may be suggested to patients who have fewer than four sites of metastases or are unable/unwilling to tolerate the potential toxicity of chemotherapy.**
- **Multiple phase III clinical trials are investigating novel combinations of ADT and androgen axis inhibitors, including enzalutamide, apalutamide, darolutamide, and orteronel without corticosteroids in mCSPC.**
- **Clinical studies suggest that addition of surgery and/or radiotherapy to systemic treatment may have a role in the treatment of newly diagnosed mCSPC, and clinical trials are investigating this hypothesis.**

Androgen-Deprivation Therapy Plus Docetaxel

To date, three clinical trials have investigated the efficacy of ADT plus docetaxel: CHAARTED, STAMPEDE arm C, and GETUG-AFU 15. CHAARTED was a phase III clinical trial that randomly assigned 790 men with mCSPC to receive ADT plus docetaxel or ADT alone.[7] Docetaxel without daily prednisone was administered every 3 weeks for a total of six cycles. The primary outcome, median OS, was 13.6 months longer for patients treated with ADT plus docetaxel than for patients receiving ADT alone (57.6 months vs. 44.0 months, respectively; HR 0.61; 95% CI, 0.47–0.80). Of note, a substantial number of patients in the ADT-alone arm never received docetaxel at CRPC before death. ADT plus docetaxel also improved median time to progression compared with ADT alone (20.2 months vs. 11.7 months; HR 0.61; 95% CI, 0.51–0.72). Docetaxel has a significant toxicity profile that differs from that of ADT, and 29.3% of patients treated with ADT plus docetaxel reported any grade 3/4 adverse events. The most frequently reported grade 3/4 adverse

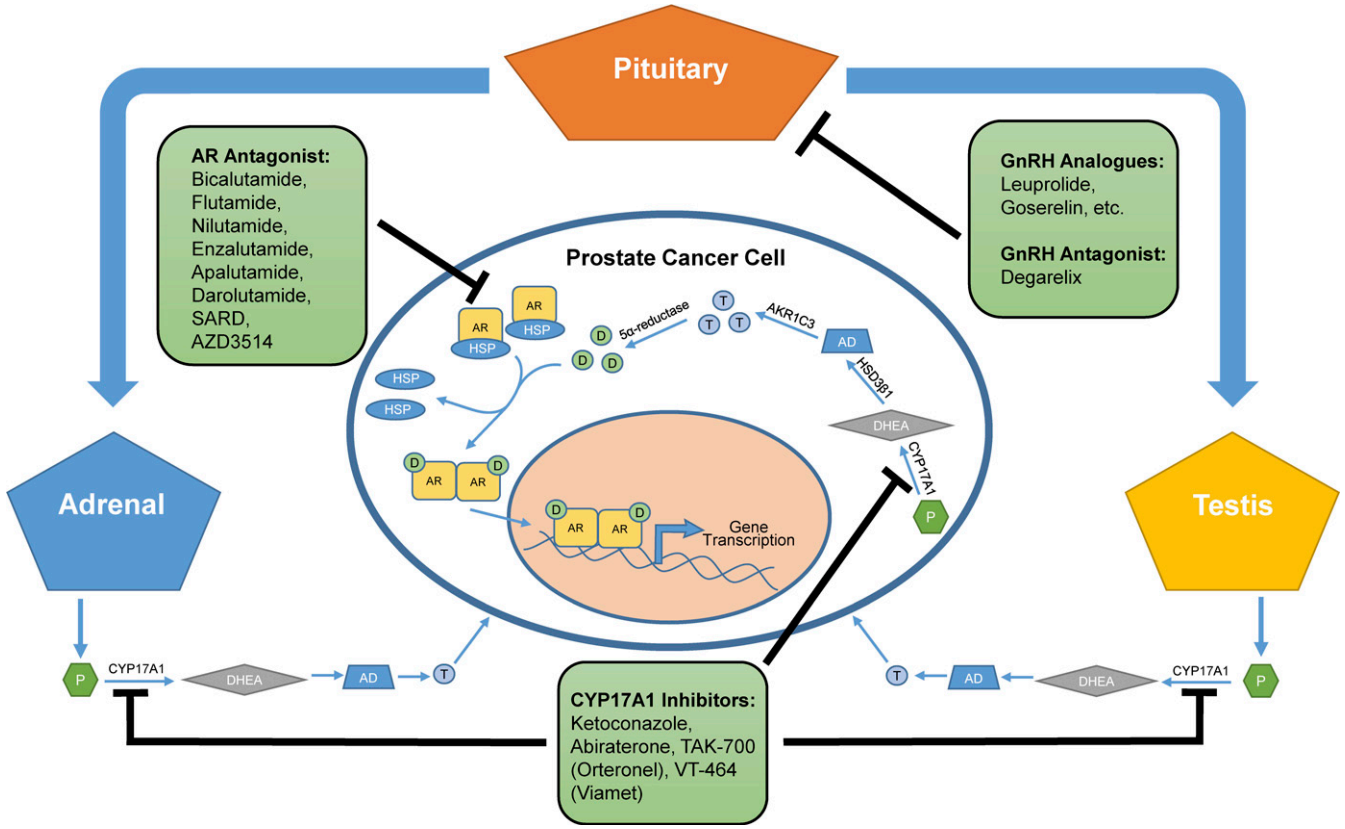
events were neutropenia (12.1%) and fatigue (4.1%). To determine whether ADT plus docetaxel should be used in all patients with mHSPC or only higher-risk patients, CHAARTED performed a subgroup analysis of median OS by extent of disease present.[19] Investigators found that only patients with high-volume disease, defined as the presence of visceral metastases or at least four bone lesions with one or more beyond the vertebral bodies and pelvis, benefit from ADT plus docetaxel (median OS, 51 months vs. 34 months; HR 0.63; 95% CI, 0.50–0.79), whereas low-volume patients have similar outcomes with ADT alone or with docetaxel (median OS, 64 months vs. not reached; HR 1.04; 95% CI, 0.70–1.55).

GETUG-AFU 15, conducted before CHAARTED, was a phase III clinical trial that randomly assigned 385 men with mCSPC to receive ADT alone or ADT plus docetaxel.[20] Median OS was not significantly improved in the ADT plus docetaxel arm compared with ADT alone (58.9 months vs. 54.2 months; HR 1.01; 95% CI, 0.75–1.36). Furthermore, before use of granulocyte colony-stimulating factor, four treatment-related deaths occurred in the ADT plus docetaxel arm. After publication of CHAARTED, a follow-up analysis of GETUG-AFU 15 reported median OS by volume of disease, which was collected retrospectively.[21] A nonsignificant trend toward improved OS was seen in high-volume disease (39.8 months vs. 35.1 months; HR 0.78; 95% CI, 0.56–1.09), and no difference in OS was observed for low-volume disease (not reached vs. 83.4 months; HR 1.02; 95% CI, 0.67–1.55).[22]

With discordant findings between CHAARTED and GETUG-AFU 15, STAMPEDE arm C sought to further explore whether ADT plus docetaxel improves survival for patients with mCSPC. STAMPEDE randomly assigned 2,962 men with locally advanced or mHSPC to receive ADT alone (arm A); ADT plus zoledronic acid (arm B); ADT plus docetaxel (arm C); or ADT, docetaxel, and zoledronic acid (arm E).[8] Similar to CHAARTED, ADT plus docetaxel significantly improved median OS compared with ADT alone in STAMPEDE arm C (81 months vs. 71.3 months; HR 0.78; 95% CI, 0.66–0.93). ADT plus docetaxel also improved median failure-free survival compared with ADT alone (37 months vs. 20 months; HR 0.61; 95% CI, 0.53–0.70). As was seen in the other trials, more patients in the ADT plus docetaxel arm reported grade 3/4 adverse events than did those receiving ADT alone (39% vs. 17%), and one treatment-related death occurred in the ADT plus docetaxel cohort. Unfortunately, STAMPEDE did not report outcomes by volume of disease.

In a meta-analysis that included CHAARTED, STAMPEDE arm C/E, and GETUG-AFU 15, ADT plus docetaxel was confirmed to significantly improve median OS (HR 0.77; 95% CI, 0.68–0.87) and median failure-free survival (HR 0.64; 95% CI, 0.58–0.70) compared with ADT alone.[23] These trials and subsequent meta-analysis established ADT plus docetaxel as a standard of care for fit patients with high-volume mCSPC.

FIGURE 1. Androgen Synthesis Pathway Throughout Body With Drugs Targeting Androgen Synthesis



Abbreviations: AR, androgen receptor; GnRH, gonadotropin-releasing hormone; HSP, heat shock protein; SARD, selective androgen receptor degrader.

ADT Plus Abiraterone Acetate Plus Prednisone

Similar to docetaxel, abiraterone acetate was initially approved for the treatment of mCRPC.[24,25] Abiraterone is a nonsteroidal, irreversible inhibitor of CYP17A1, so it inhibits gonadal and extragonadal androgen synthesis. To date, two clinical trials studying abiraterone in mCSPC have been reported, LATITUDE and STAMPEDE arm G; one study, PEACE-1, is still ongoing. LATITUDE was a phase III clinical trial that randomly assigned 1,199 men with mCSPC to receive ADT plus abiraterone (1,000 mg daily) and prednisone (5 mg daily) or ADT alone.[9] To be included in the trial, men with mCSPC needed to have at least two high-risk prognostic factors, including a Gleason score of 8 or higher, presence of at least three bone lesions, or measurable visceral metastases. LATITUDE was powered to measure two primary endpoints: median OS and radiographic progression-free survival. ADT plus abiraterone significantly improved median OS (not reached vs. 34.7 months; HR 0.62; 95% CI, 0.51–0.76) and median radiographic progression-free survival (33.0 vs. 14.8 months; HR 0.47; 95% CI, 0.39–0.55). Regarding toxicity, grade 3/4 adverse events were more common in the ADT plus abiraterone arm (63% vs. 48%). The most frequently reported grade 3/4 adverse events in the abiraterone arm were mineralocorticoid-related hypertension (20%), hypokalemia (11%), and increased alanine aminotransferase levels (5%).

Interestingly, in 2017, STAMPEDE arm G, which was simultaneously presented with LATITUDE at the ASCO annual meeting, showed similar benefits with upfront abiraterone. STAMPEDE arm G was a phase III clinical trial that included multiple cohorts of patients with advanced prostate cancer, including mCSPC, node-positive disease, or high-risk locally advanced disease.[10] In total, 1,917 men with advanced prostate cancer were randomly assigned to receive ADT plus 1,000 mg of abiraterone plus 5 mg of prednisolone or ADT alone. Of these 1,917 men, 941 had newly diagnosed mCSPC. In the overall cohort, ADT plus abiraterone demonstrated a strong OS advantage compared with ADT (83% vs. 76%; HR 0.63; 95% CI, 0.52–0.76) and better 3-year failure-free survival (75% vs. 45%; HR 0.29; 95% CI, 0.25–0.34). In patients with mCSPC, the effect of ADT plus abiraterone on OS and failure-free survival remained true. As was seen in LATITUDE, the incidence of grade 3/4 adverse events was higher in the ADT plus abiraterone group than in the ADT-alone group (47% vs. 33%). On the basis of the results from the LATITUDE and STAMPEDE arm G clinical trials, ADT plus abiraterone acetate and prednisone is now considered a standard of care for mCSPC regardless of the disease volume status. However, follow-up for nonmetastatic prostate cancer is not adequate to determine the benefit.

A third phase III clinical trial evaluating ADT plus abiraterone is in progress. PEACE-1 will randomly assign 916 patients with mCSPC to one of four arms: ADT with or without docetaxel, ADT with or without docetaxel and abiraterone and prednisone, ADT with or without docetaxel and radiotherapy, or ADT with or without docetaxel and abiraterone and prednisone. PEACE-1 will help us better understand whether docetaxel and abiraterone can have synergistic effect in mCSPC.

OPTIMAL CURRENT TREATMENT PARADIGM

Because clinical trials investigating ADT plus docetaxel and ADT plus abiraterone had very similar outcomes and head-to-head, prospective comparisons were not performed, clinicians face a new challenge optimizing treatment selection for patients with mCSPC. Furthermore, predictive biomarkers are not available in the clinic to help guide treatment selection. Although the efficacy of these regimens is similar, the toxicity profiles, cost, and duration of treatment can help guide selection between docetaxel and abiraterone.

Analysis of the individual trials shows that the disease volume may help tailor treatment selection.[26] In CHAARTED and GETUG-AFU 15, men with low-volume disease did not benefit with docetaxel. However, none of the trials with abiraterone have categorized men according to the volume status of the disease and thus have not shown lack of benefit in any given subset of patients.[27] We recommend that docetaxel be considered for patients with high-volume disease, and abiraterone can be recommended to all regardless of disease volume (Table 1). Table 1 shows considerations for the treating physician choosing between ADT plus abiraterone and ADT plus docetaxel.

In regard to toxicity, the frequency of grade 3 to 5 adverse events was similar between ADT plus docetaxel and ADT plus abiraterone plus prednisone. However, the profile of adverse events significantly differs between the two drugs. Docetaxel may cause bone marrow suppression, infections, and neuropathy, whereas abiraterone may cause mineralocorticoid-induced hypertension, hypokalemia, and elevated liver enzyme levels. In general, most patients better tolerate abiraterone than docetaxel. The duration of treatment also differs significantly between the reported regimens of docetaxel and abiraterone in mCSPC. Docetaxel is given once every 3 weeks for a total of six cycles, which is generally around 15 weeks of total treatment. In contrast, abiraterone is recommended daily until time of progression, which generally occurs after several years of treatment with abiraterone. Finally, the expense to the patient of abiraterone and docetaxel differs significantly. When only cost per cycle and number of cycles given are considered, the six cycles of docetaxel cost the same as 3- to 4-month treatment

TABLE 1. Attributes of Treatment That Favor ADT Plus Abiraterone or ADT Plus Docetaxel

Attribute	Favors Abiraterone	Favors Docetaxel
Efficacy in HVD	X	X
Efficacy in LVD	X	
Toxicity	X	
Treatment duration		X
Cost		X

Abbreviations: ADT, androgen-deprivation therapy; HVD, high-volume disease; LVD, low-volume disease.

TABLE 2. Ongoing and Recently Reported Phase III Clinical Trials Evaluating Novel Androgen Axis Inhibitors in Metastatic Hormone-Sensitive Prostate Cancer

Trial Name	Arms	No. of Patients	Primary Endpoint	ClinicalTrials.gov Identifier	Anticipated Read Out
PEACE-1	ADT ± doce, ± RT, ± abi	916	rPFS, OS	NCT01957436	2020
SWOG-1216	ADT + TAK-700 vs. bicalutamide	1,304	OS	NCT01809691	2020
ARASENS	ADT + doce + ODM-201 vs. placebo	1,300	OS	NCT02799602	2022
ENZA-MET	ADT ± doce + enza vs. NSAA	1,100	OS	NCT02446405	2020
ARCHES	ADT ± doce + enza vs. placebo	1,100	rPFS	NCT02677896	2023
STAMPEDE ARM J	ADT ± doce, ± RT, ± abi + enza	1,800	OS	NCT00268476	2020
TITAN	ADT ± doce + apa vs. placebo	1,000	rPFS, OS	NCT02489318	2021

Abbreviations: ADT, androgen-deprivation therapy; doce, docetaxel; RT, radiotherapy; abi, abiraterone acetate; rPFS, radiographic progression-free survival; OS, overall survival; enza, enzalutamide; NSAA, nonsteroidal androgen antagonist; apa, apalutamide.

with abiraterone. Additionally, there is frequently a high copay with abiraterone (an oral drug) compared with docetaxel (an intravenous drug).[28,29] This is a simplistic analysis that does not account for many components of cost-effectiveness; however, a formal cost-effectiveness analysis has yet to be done. Thus, docetaxel may be favored over abiraterone for patients or in countries where cost factors heavily into the treatment decision.

In summary, ADT plus docetaxel may be considered for patients who desire shorter total treatment time or when there are cost considerations. ADT plus abiraterone can be considered in patients who have low-volume disease, desire to avoid possible chemotherapy toxicity, or want to minimize facility visits for docetaxel administration. Finally, patient-specific comorbidities may guide treatment selection, for example, avoiding docetaxel in frail patients at high risk for myelosuppression and those with neuropathy and avoiding abiraterone plus prednisone in those with liver disease, diabetes, and osteoporosis.

NOVEL COMBINATIONS BEING INVESTIGATED FOR METASTATIC CASTRATION-SENSITIVE PROSTATE CANCER

With the knowledge that deeper androgen signaling blockade leads to improved outcomes in mCSPC and the recent success of docetaxel and abiraterone, several novel combinations of ADT plus androgen axis inhibitors are under investigation. Enzalutamide is a second-generation antiandrogen that binds to the AR with higher affinity than bicalutamide and prevents nuclear translocation of the AR (Fig. 1).[30] Enzalutamide is approved as any-line treatment of mCRPC.[31,32] Two phase III clinical trials are evaluating ADT plus enzalutamide in patients with mCSPC: ENZA-MET and ARCHES (Table 2). ENZA-MET (NCT02446405) will randomly assign 1,000 patients with mCSPC to receive ADT with or without docetaxel plus enzalutamide or ADT with or without docetaxel plus a nonsteroidal androgen antagonist. ENZA-MET is anticipated to read out in 2020, and it will tell us whether ADT plus enzalutamide is more efficacious than standard ADT and whether ADT plus enzalutamide has a synergistic effect with docetaxel. ARCHES (NCT02677896) aims to answer the same clinical questions. ARCHES is also randomly assigning 1,100 patients to receive ADT with or without docetaxel plus enzalutamide or ADT with or without docetaxel plus placebo. Unfortunately, neither of these trials is comparing ADT plus enzalutamide to ADT plus abiraterone or docetaxel, which are now considered standard of care.

Apalutamide (ARN-509) is another second-generation antiandrogen that is an irreversible AR antagonist. Recently, in the SPARTAN trial in men with M0 CRPC, apalutamide showed improved survival outcomes; however, it is not currently approved for prostate cancer.[33] ADT plus apalutamide is being studied for mCSPC in the phase III TITAN clinical trial (NCT02489318). Previously, a phase II clinical trial of apalutamide in mCRPC demonstrated acceptable safety and efficacy to warrant further investigations in mCSPC and mCRPC.[34] TITAN is randomly assigning 1,000 patients with mCSPC to receive ADT with or without docetaxel plus apalutamide versus ADT alone (Table 2). TITAN will answer the question of whether addition of apalutamide to standard-of-care treatment may improve survival outcomes in mCSPC.

Darolutamide (ODM-201) is a next-generation antiandrogen that has a higher affinity for the AR than does enzalutamide or apalutamide.[35] Darolutamide is not currently approved for the treatment of prostate cancer. However, a phase I/II clinical trial in 134 men with progressive mCRPC found darolutamide to have an acceptable safety profile.[36] ARASENS (NCT02799602) is a phase III clinical trial in mCSPC that will randomly assign 1,300 men to receive ADT plus docetaxel and either darolutamide or placebo (Table 2). ARASENS is expected to read out in 2022.

Orteronel (TAK-700) is unique from the other novel androgen axis inhibitors discussed because it is a reversible CYP17 inhibitor that has more specificity for 17,20 lyase than 17 hydroxylase. Preclinical studies demonstrated that orteronel significantly reduces testosterone and androstenedione levels in cell lines and rats, resulting in smaller prostates.[37,38] Although phase III clinical trials in mCRPC showed no OS benefit with orteronel, a phase II trial in patients with nonmetastatic prostate cancer and biochemical recurrence

found that orteronel decreased PSA by greater than 30% in most patients and that 16% achieved a PSA less than 0.2 ng/mL at 3 months.[39-41] A phase III clinical trial, SWOG-1216, is investigating ADT plus orteronel (without prednisone) compared with ADT plus bicalutamide in 1,304 patients with mCSPC (NCT01809691).

THE ROLE OF LOCALIZED THERAPY IN METASTATIC CASTRATION-SENSITIVE PROSTATE CANCER

Prostate radiation or radical prostatectomy (RP) are not currently recommended for the treatment of patients with de novo metastatic prostate cancer. In some advanced malignancies, such as metastatic renal cell carcinoma, patients experience a survival benefit from cytoreductive surgery, which is considered a standard of care for these patients.[42] This has led to increased interest in the role of local therapy for mCSPC. Although reported studies have important limitations, early results for this approach in mCSPC are intriguing and warrant further investigation.

Initially, two hypothesis-generating, retrospective Surveillance, Epidemiology, and End Results (SEER) database studies found that local therapy combined with systemic therapy improved survival in metastatic prostate cancer. In the first SEER analysis, 8,185 patients with stage IV prostate cancer were identified between 2004 and 2010.[43] Of these 8,185 patients, 245 patients (3.0%) had an RP performed, and 129 patients (1.6%) were treated with prostate brachytherapy. The remaining, untreated patients were significantly older ($p < .001$) and less likely to have a Gleason score of 7 or lower ($p < .001$). Five-year OS and cancer-specific survival were higher in patients receiving RP (67.4% and 75.8%, respectively) and brachytherapy (52.6% and 61.3%) than in those receiving no local treatment (22.5% and 48.7%; $p < .001$). Another SEER study used a propensity score analysis to ensure that the observed effect of radical prostatectomy or brachytherapy were attributable to treatment instead of baseline cohort differences.[44] The authors confirmed that RP and brachytherapy improve CSS compared with no definitive treatment. Because of their use of the SEER database, both studies had substantial limitations, including not accounting for whether patients received ADT and the fact that less than 5% of their total cohorts received definitive therapy.[45] A third retrospective study used the National Cancer Database to confirm the findings from previous SEER studies.[46] Of 6,382 men with newly diagnosed mCSPC in this database, 538 men (8.4%) were treated with ADT plus radiotherapy, and the remaining men were treated with ADT alone. Men treated with ADT plus radiotherapy had significantly improved OS in multivariate analysis (HR 0.62; 95% CI, 0.55–0.71).

To address the limitations of the prior SEER studies, a study linked SEER outcomes to Medicare data.[47] This study design allowed the authors to account for medical comorbidities, receipt of ADT, and type of radiotherapy given (palliative, localized intensity-modulated radiation, or conformal radiation). In the multivariate analysis accounting for these factors, prostate cancer–specific mortality was improved for RP (HR 0.48; 95% CI, 0.27–0.85) and intensity-modulated radiation (HR 0.38; 95% CI, 0.24–0.61). Because the three prior studies came from the U.S. SEER database, a retrospective study of the Munich Cancer registry also looked at the effect of RP on survival for mCSPC.[48] Of the 1,538 men with mCSPC, 75 men (5%) received RP, and this group had improved 5-year OS compared with the no-surgery arm (55% vs. 21%; $p < .01$). Finally, a case-control series of 140 men with mCSPC randomly assigned 38 men to prostate radiotherapy, 39 to palliative radiotherapy, and 63 to no radiotherapy.[49] Patients who received prostate radiotherapy had improved 3-year OS compared with the other groups (69% vs. 43%; $p = .004$), and no grade 3 or worse genitourinary adverse events were reported.

In summary, RP and local radiotherapy have shown potential to improve survival in patients with mCSPC.[50] However, the design of reported studies (i.e., retrospective or case-control series) and inconsistent findings indicate that randomized clinical trials are needed before definitive therapy is routinely used in the management of newly diagnosed mCSPC. A phase II clinical trial randomly assigning 180 men with mCSPC to ADT with or without localized therapy (NCT01751438) is underway and should begin to address this hypothesis. As clinical trials investigate these questions, investigators must consider how the significant morbidity associated with definitive therapy weighs against the benefits of treatment.

METASTASIS-DIRECTED THERAPY FOR OLIGOMETASTATIC PROSTATE CANCER

Although no consensus definition exists, oligometastatic prostate cancer is often defined as at least three or five metastases.[51] To date, it is unclear whether patients with oligometastatic prostate cancer should be treated differently than patients with high-volume disease.

Multiple retrospective studies initially suggested that metastasis-directed therapy is safe, feasible, and efficacious in patients with oligometastatic prostate cancer. In a single-center study of 40 patients with fewer than two bone metastases in the spine, stereotactic body radiation therapy (SBRT) to the metastatic lesions was associated with an estimated local disease control rate of 95.5% at 6, 12, and 24 months.[52] Another single-center study of 21 patients with oligometastatic disease involving the bone (19 patients), lymph nodes (one patient), or liver (one patient) found that SBRT had 100% local control at 5 months and that 53% of patients had an undetectable PSA.[53] These studies were followed by a multicenter retrospective study of 119 patients that confirmed SBRT is efficacious in oligometastatic prostate cancer.[54] Then, two retrospective studies demonstrated that SBRT delays the initiation of ADT for patients with oligometastatic disease.[55,56]

With multiple retrospective studies suggesting that metastasis-directed therapy may be efficacious for oligometastatic prostate cancer, a phase II clinical trial, STOMP, sought to validate the role for metastasis-directed therapy.[57] In STOMP, 62 patients with biochemical recurrence after

definitive therapy or fewer than three extracranial metastatic lesions were randomly assigned to surveillance or metastasis-directed therapy (either SBRT or surgery). The median ADT-free survival for surveillance was 13 months compared with 21 months for the metastasis-directed therapy arm (HR 0.60; 95% CI, 0.40–0.90). Quality of life was similar in the two arms at baseline, 3 months, and 12 months. Two ongoing phase III clinical trials, CORE and PCX IX, will provide overall survival data for metastasis-directed therapy. CORE (NCT02759783) is randomly assigning 206 patients with oligometastatic prostate, breast, and non–small cell lung cancer to standard of care or standard of care plus SBRT. In contrast, PCX IX (NCT02685397) is randomly assigning 130 patients with oligometastatic CRPC to an LHRH agonist plus enzalutamide or to LHRH agonist plus enzalutamide plus SBRT.

CONCLUSION

ADT plus docetaxel and ADT plus abiraterone are the contemporary standard treatment of mCSPC. ADT plus docetaxel may be considered for patients with mCSPC who have good performance status, have high-volume disease, desire shorter total treatment time, or have concerns of prescription drug costs. ADT plus abiraterone acetate may be suggested for men with cancer of any volume and who desire to minimize hospital visits associated with chemotherapy infusions. Patient-specific comorbidities may guide treatment selection as well; for example, abiraterone plus prednisone may be avoided in those with diabetes, liver disease, osteoporosis, or difficult-to-control hypertension, and docetaxel may be avoided in those with neuropathy or at high risk for myelosuppression. Eventually, we need predictive biomarkers to optimize treatment selection between these current and emerging therapies. We also anticipate that treatment of mCSPC will continue to rapidly evolve. Multiple novel androgen axis inhibitors are being investigated in combination with ADT for treatment of mCSPC. On the basis of retrospective and case-control series data, local therapy for de novo mCSPC has the potential to augment current systemic therapies. Finally, for patients with oligometastatic prostate cancer, metastasis-directed therapy combined with systemic therapy is promising.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin*. 2018;68:7-30.
2. Jemal A, Fedewa SA, Ma J, et al. Prostate cancer incidence and PSA testing patterns in relation to USPSTF screening recommendations. *JAMA*. 2015;314:2054-2061.
3. Weiner AB, Matulewicz RS, Eggener SE, et al. Increasing incidence of metastatic prostate cancer in the United States (2004-2013). *Prostate Cancer Prostatic Dis*. 2016;19:395-397.
4. Dalela D, Sun M, Diaz M, et al. Contemporary trends in the incidence of metastatic prostate cancer among US men: results from nationwide analyses. *Eur Urol Focus*.
5. National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Cancer Stat Facts. Prostate Cancer. https://seer.cancer.gov/statfacts/html/prost.html. Accessed January 7, 2018.
6. Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. 1941. *J Urol*. 2002;167:948-951, discussion 952.
7. Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *N Engl J Med*. 2015;373:737-746.
8. James ND, Sydes MR, Clarke NW, et al. STAMPEDE investigators. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *Lancet*. 2016;387:1163-1177.
9. Fizazi K, Tran N, Fein L, et al. LATITUDE Investigators. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. *N Engl J Med*. 2017;377:352-360.
10. James ND, de Bono JS, Spears MR, et al. STAMPEDE Investigators. Abiraterone for prostate cancer not previously treated with hormone therapy. *N Engl J Med*. 2017;377:338-351.
11. Massie CE, Lynch A, Ramos-Montoya A, et al. The androgen receptor fuels prostate cancer by regulating central metabolism and biosynthesis. *EMBO J*. 2011;30:2719-2733.
12. Harris WP, Mostaghel EA, Nelson PS, et al. Androgen deprivation therapy: progress in understanding mechanisms of resistance and optimizing androgen depletion. *Nat Clin Pract Urol*. 2009;6:76-85.
13. Clinton TN, Woldu SL, Raj GV. Degarelix versus luteinizing hormone-releasing hormone agonists for the treatment of prostate cancer. *Expert Opin Pharmacother*. 2017;18:825-832.
14. Seidenfeld J, Samson DJ, Hasselblad V, et al. Single-therapy androgen suppression in men with advanced prostate cancer: a systematic review and meta-analysis. *Ann Intern Med*. 2000;132:566-577.
15. Hussain M, Tangen CM, Berry DL, et al. Intermittent versus continuous androgen deprivation in prostate cancer. *N Engl J Med*. 2013;368:1314-1325.
16. Hussain M, Tangen CM, Higano C, et al; Southwest Oncology Group Trial 9346 (INT-0162). Absolute prostate-specific antigen value after androgen deprivation is a strong independent predictor of survival in new metastatic prostate cancer: data from Southwest Oncology Group Trial 9346 (INT-0162). *J Clin Oncol*. 2006;24:3984-3990.
17. Klotz L, O'Callaghan C, Ding K, et al. Nadir testosterone within first year of androgen-deprivation therapy (ADT) predicts for time to castration-resistant progression: a secondary analysis of the PR-7 trial of intermittent versus continuous ADT. *J Clin Oncol*. 2015;33:1151-1156.
18. Hahn AW, Hale P, Rathi N, et al. Novel androgen axis systemic therapies for metastatic hormone-sensitive prostate cancer. *Curr Opin Urol*. 2017;27:559-565.
19. Sweeney C, Chen Y, Liu G, et al. Long term efficacy and QOL data of chemohormonal therapy in low and high volume hormone naïve metastatic prostate cancer: E3805 CHAARTED trial. *Ann Oncol*. 2016;27(suppl_6):243-265.

20. Gravis G, Fizazi K, Joly F, et al. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2013;14:149-158.

21. Gravis G, Boher JM, Joly F, et al; GETUG. Androgen deprivation therapy (ADT) plus docetaxel versus ADT alone in metastatic non castrate prostate cancer: impact of metastatic burden and long-term survival analysis of the randomized phase 3 GETUG-AFU15 Trial. *Eur Urol*. 2016;70:256-262.

22. Sridhar SS, Sweeney CJ. It is time to harmonize the design and conduct of clinical trials in metastatic hormone-sensitive prostate cancer. *Eur Urol*. 2016;70:263-264.

23. Vale CL, Burdett S, Rydzewska LHM, et al; STOpCaP Steering Group. Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: a systematic review and meta-analyses of aggregate data. *Lancet Oncol*. 2016;17:243-256.

24. de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med*. 2011;364:1995-2005.

25. Ryan CJ, Smith MR, de Bono JS, et al; COU-AA-302 Investigators. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med*. 2013;368:138-148.

26. Aggarwal R. Abiraterone or docetaxel plus androgen deprivation in hormone-sensitive prostate cancer: more questions than answers. *Eur Urol*. Epub 2017 Nov 8.

27. James N, de Bono J, Spears MR, et al. Adding abiraterone for patients with high-risk prostate cancer starting long-term androgen deprivation therapy: outcomes in non-metastatic (M0) patients from STAMEPE (NCT00268476). *Ann Oncol*. 2017;(Suppl 5):LBA34.

28. Pollard ME, Moskowitz AJ, Diefenbach MA, et al. Cost-effectiveness analysis of treatments for metastatic castration resistant prostate cancer. *Asian J Urol*. 2017;4:37-43.

29. McNamara M, Sweeney C, Antonarakis ES, et al. The evolving landscape of metastatic hormone-sensitive prostate cancer: a critical review of the evidence for adding docetaxel or abiraterone to androgen deprivation. *Prostate Cancer Prostatic Dis.* Epub 2017 Dec 20.

30. Agarwal N, Hussain M. Management of hormone-sensitive metastatic prostate cancer. *Hematol Oncol Clin North Am*. 2013;27:1221-1241, viii.

31. Scher HI, Fizazi K, Saad F, et al; AFFIRM Investigators. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med*. 2012;367:1187-1197.

32. Beer TM, Armstrong AJ, Rathkopf DE, et al; PREVAIL Investigators. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med*. 2014;371:424-433.

33. Small EJ, Saad F, Chowdhury S, et al. SPARTAN, a phase 3 double-blind, randomized study of apalutamide (APA) versus placebo (PBO) in patients (pts) with nonmetastatic castration-resistant prostate cancer (nmCRPC). *J Clin Oncol*. 2018;36 (6 suppl; abstr 161).

34. Rathkopf DE, Antonarakis ES, Shore ND, et al. Safety and antitumor activity of apalutamide (ARN-509) in metastatic castration-resistant prostate cancer with and without prior abiraterone acetate and prednisone. *Clin Cancer Res*. 2017;23:3544-3551.

35. Shore ND. Darolutamide (ODM-201) for the treatment of prostate cancer. *Expert Opin Pharmacother*. 2017;18:945-952.

36. Fizazi K, Massard C, Bono P, et al; ARADES study group. Activity and safety of ODM-201 in patients with progressive metastatic castration-resistant prostate cancer (ARADES): an open-label phase 1 dose-escalation and randomised phase 2 dose expansion trial. *Lancet Oncol*. 2014;15:975-985.

37. Yamaoka M, Hara T, Hitaka T, et al. Orteronel (TAK-700), a novel non-steroidal 17,20-lyase inhibitor: effects on steroid synthesis in human and monkey adrenal cells and serum steroid levels in cynomolgus monkeys. *J Steroid Biochem Mol Biol*. 2012;129:115-128.

38. Hara T, Kouno J, Kaku T, et al. Effect of a novel 17,20-lyase inhibitor, orteronel (TAK-700), on androgen synthesis in male rats. *J Steroid Biochem Mol Biol*. 2013;134:80-91.

39. Hussain M, Corn PG, Michaelson MD, et al; Prostate Cancer Clinical Trials Consortium, a program of the Department of Defense Prostate Cancer Research Program and the Prostate Cancer Foundation. Phase II study of single-agent orteronel (TAK-700) in patients with nonmetastatic castration-resistant prostate cancer and rising prostate-specific antigen. *Clin Cancer Res*. 2014;20:4218-4227.

40. Fizazi K, Jones R, Oudard S, et al. Phase III, randomized, double-blind, multicenter trial comparing orteronel (TAK-700) plus prednisone with placebo plus prednisone in patients with metastatic castration-resistant prostate cancer that has progressed during or after docetaxel-based therapy: ELM-PC 5. *J Clin Oncol*. 2015;33:723-731.

41. Saad F, Fizazi K, Jinga V, et al; ELM-PC 4 Investigators. Orteronel plus prednisone in patients with chemotherapy-naive metastatic castration-resistant prostate cancer (ELM-PC 4): a double-blind, multicentre, phase 3, randomised, placebo-controlled trial. *Lancet Oncol*. 2015;16:338-348.

42. Lenis AT, Salmasi AH, Donin NM, et al. Trends in usage of cytoreductive partial nephrectomy and effect on overall survival in patients with metastatic renal cell carcinoma. *Urol Oncol*. 2018;36:78.e21-78.e28.

43. Culp SH, Schellhammer PF, Williams MB. Might men diagnosed with metastatic prostate cancer benefit from definitive treatment of the primary tumor? A SEER-based study. *Eur Urol*. 2014;65:1058-1066.

44. Antwi S, Everson TM. Prognostic impact of definitive local therapy of the primary tumor in men with metastatic prostate cancer at diagnosis: a population-based, propensity score analysis. *Cancer Epidemiol*. 2014;38:435-441.

45. Tosoian JJ, Gorin MA, Ross AE, et al. Oligometastatic prostate cancer: definitions, clinical outcomes, and treatment considerations. *Nat Rev Urol*. 2017;14:15-25.

46. Rusthoven CG, Jones BL, Flaig TW, et al. Improved survival with prostate radiation in addition to androgen deprivation therapy for men with newly diagnosed metastatic prostate cancer. *J Clin Oncol*. 2016;34:2835-2842.

47. Satkunasivam R, Kim AE, Desai M, et al. Radical prostatectomy or external beam radiation therapy vs no local therapy for survival benefit in metastatic prostate cancer: a SEER-Medicare analysis. *J Urol*. 2015;194:378-385.

48. Gratzke C, Engel J, Stief CG. Role of radical prostatectomy in metastatic prostate cancer: data from the Munich Cancer Registry. *Eur Urol*. 2014;66:602-603.

49. Cho Y, Chang JS, Rha KH, et al. Does radiotherapy for the primary tumor benefit prostate cancer patients with distant metastasis at initial diagnosis? *PLoS One*. 2016;11:e0147191.

50. Metcalfe MJ, Smaldone MC, Lin DW, et al. Role of radical prostatectomy in metastatic prostate cancer: a review. *Urol Oncol*. 2017;35:125-134.

51. Kim J, Park JS, Ham WS. The role of metastasis-directed therapy and local therapy of the primary tumor in the management of oligometastatic prostate cancer. *Investig Clin Urol*. 2017;58: 307-316.

52. Muacevic A, Kufeld M, Rist C, et al. Safety and feasibility of image-guided robotic radiosurgery for patients with limited bone metastases of prostate cancer. *Urol Oncol*. 2013;31:455-460.

53. Ahmed KA, Barney BM, Davis BJ, et al. Stereotactic body radiation therapy in the treatment of oligometastatic prostate cancer. *Front Oncol*. 2013;2:215.

54. Ost P, Jereczek-Fossa BA, As NV, et al. Progression-free survival following stereotactic body radiotherapy for oligometastatic prostate cancer treatment-naive recurrence: a multi-institutional analysis. *Eur Urol*. 2016;69:9-12.

55. Berkovic P, De Meerleer G, Delrue L, et al. Salvage stereotactic body radiotherapy for patients with limited prostate cancer metastases: deferring androgen deprivation therapy. *Clin Genitourin Cancer*. 2013;11:27-32.

56. Decaestecker K, De Meerleer G, Lambert B, et al. Repeated stereotactic body radiotherapy for oligometastatic prostate cancer recurrence. *Radiat Oncol*. 2014;9:135.

57. Ost P, Reynders D, Decaestecker K, et al. Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: a prospective, randomized, multicenter phase II trial. *J Clin Oncol*. 2018;36:446-453.

JAMA Oncology | Original Investigation

Radiographic Progression-Free Survival as a Clinically Meaningful End Point in Metastatic Castration-Resistant Prostate Cancer

The PREVAIL Randomized Clinical Trial

Dana E. Rathkopf, MD; Tomasz M. Beer, MD; Yohann Loriot, MD, PhD; Celestia S. Higano, MD; Andrew J. Armstrong, MD, ScM; Cora N. Sternberg, MD; Johann S. de Bono, MB ChB, PhD; Bertrand Tombal, MD, PhD; Teresa Parli, MD; Suman Bhattacharya, PhD; De Phung, BSc; Andrew Krivoshik, MD, PhD; Howard I. Scher, MD; Michael J. Morris, MD

IMPORTANCE Drug development for metastatic castration-resistant prostate cancer has been limited by a lack of clinically relevant trial end points short of overall survival (OS). Radiographic progression-free survival (rPFS) as defined by the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) is a candidate end point that represents a clinically meaningful benefit to patients.

OBJECTIVE To demonstrate the robustness of the PCWG2 definition and to examine the relationship between rPFS and OS.

DESIGN, SETTING, AND PARTICIPANTS PREVAIL was a phase 3, randomized, double-blind, placebo-controlled multinational study that enrolled 1717 chemotherapy-naive men with metastatic castration-resistant prostate cancer from September 2010 through September 2012. The data were analyzed in November 2016.

INTERVENTIONS Patients were randomized 1:1 to enzalutamide 160 mg or placebo until confirmed radiographic disease progression or a skeletal-related event and initiation of either cytotoxic chemotherapy or an investigational agent for prostate cancer treatment.

MAIN OUTCOMES AND MEASURES Sensitivity analyses (SAs) of investigator-assessed rPFS were performed using the final rPFS data cutoff (May 6, 2012; 439 events; SA1) and the interim OS data cutoff (September 16, 2013; 540 events; SA2). Additional SAs using investigator-assessed rPFS from the final rPFS data cutoff assessed the impact of skeletal-related events (SA3), clinical progression (SA4), a confirmatory scan for soft-tissue disease progression (SA5), and all deaths regardless of time after study drug discontinuation (SA6). Correlations between investigator-assessed rPFS (SA2) and OS were calculated using Spearman ρ and Kendall τ via Clayton copula.

RESULTS In the 1717 men (mean age, 72.0 [range, 43.0-93.0] years in enzalutamide arm and 71.0 [range, 42.0-93.0] years in placebo arm), enzalutamide significantly reduced risk of radiographic progression or death in all SAs, with hazard ratios of 0.22 (SA1; 95% CI, 0.18-0.27), 0.31 (SA2; 95% CI, 0.27-0.35), 0.21 (SA3; 95% CI, 0.18-0.26), 0.21 (SA4; 95% CI, 0.17-0.26), 0.23 (SA5; 95% CI, 0.19-0.30), and 0.23 (SA6; 95% CI, 0.19-0.30) ($P < .001$ for all). Correlations of rPFS and OS in enzalutamide-treated patients were 0.89 (95% CI, 0.86-0.92) by Spearman ρ and 0.72 (95% CI, 0.68-0.77) by Kendall τ.

CONCLUSIONS AND RELEVANCE Sensitivity analyses in PREVAIL demonstrated the robustness of the PCWG2 rPFS definition using additional measures of progression. There was concordance between central and investigator review and a positive correlation between rPFS and OS among enzalutamide-treated patients.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01212991

JAMA Oncol. 2018;4(5):694-701. doi:10.1001/jamaoncol.2017.5808
Published online March 8, 2018.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Michael J. Morris, MD, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10065 (morrism@mskcc.org).

Overall survival (OS) is the benchmark for regulatory drug approval for patients with advanced cancer. Since 2010, 5 agents have achieved the milestone of prolonging OS for men with metastatic castration-resistant prostate cancer (mCRPC), and these agents have transformed the management of the disease.[1-8] The availability of these effective therapies, although clinically beneficial to patients, can have a secondary effect of blunting the impact of an investigational agent on OS by virtue of postprotocol exposures. Consequently, development efforts focusing on OS are likely to shift to more advanced and heavily pretreated clinical settings. End points short of survival that represent clinical benefit and can independently support regulatory approval will be necessary to ensure that effective drugs are available to improve outcomes for patients across all stages of disease.

To address this, the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) developed a set of consensus criteria in 2008 regarding clinical trial conduct for contemporary studies in men with mCRPC.[9] The PCWG2 stressed the importance of time-to-event measures that are not affected by posttreatment therapies and that could be strongly linked to clinical outcomes that were indicative of a worsening disease status, including deteriorations in quality of life, a need for a change in anticancer therapy, and, ultimately, death from disease. One such end point, radiographic progression-free survival (rPFS), is not affected by postprotocol treatments, but it has been difficult to quantify because of the lack of standardization of the outcome measure itself.

The PCWG2 sought to establish a definition for rPFS that would ensure that a drug was not working before therapy was discontinued. One definition proposed by PCWG2 was a "2 + 2" rule, which stated that progression not be declared early in a patient's treatment course unless at least 2 new lesions were seen on the first on-treatment scan, followed by at least 2 additional lesions on the second posttreatment scan. The rule was designed to control for tumor flare, a paradoxical worsening of the bone scan attributed to bone healing as a result of a favorable antitumor effect.[9,10] The central hypothesis was that the continuous development of new lesions on sequential scans was an indication that the cancer was continuing to grow and spread as opposed to healing.

To enable the clinical validation of the PCWG2-proposed bone scan progression measure, a quantitative and reproducible bone scan assay was developed, analytically validated, and subsequently used as an integral part of the case report forms of serial, prospectively conducted, large phase 3 studies using androgen receptor (AR)-directed therapy.[7,11,12] The progression biomarker was used first in the COU-AA-302 study of abiraterone acetate plus prednisone in chemotherapy-naive patients with mCRPC as a component of the definition of rPFS, which was a co-primary end point of the study.[12] PREVAIL, a phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of enzalutamide in chemotherapy-naive patients with mCRPC,[7] was another trial that used rPFS as a co-primary end point with OS, allowing for further validation of the bone scan assay based on the PCWG2 criteria. As previously reported, PREVAIL demonstrated that enzalutamide therapy decreased the risk of death by 29% (hazard ratio [HR], 0.71; 95% CI, 0.60-0.84; $P < .001$) and the risk of radiographic progression by 81% (HR, 0.19; 95% CI, 0.15-0.23; $P < .001$).[7]

Key Points

Question What is the clinical relevance of the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) definition of radiographic progression-free survival (rPFS)?

Findings In a series of prespecified sensitivity analyses of rPFS in the PREVAIL randomized clinical trial of 1717 men with chemotherapy-naive metastatic castration-resistant prostate cancer, enzalutamide significantly reduced the risk of radiographic progression or death. Using 2 different statistical methods, rPFS and overall survival were found to be positively correlated.

Meaning The PCWG2 definition of rPFS is a robust end point that is clinically meaningful and associated with overall survival.

A series of sensitivity analyses (SAs) were included in the trial design of PREVAIL to evaluate how robust and clinically meaningful the rPFS result signified.[7,13] These prespecified analyses examined the impact of additional measures of progression, including skeletal-related events (SREs), initiation of radiotherapy and or new antineoplastic therapy, and unequivocal clinical progression, on the primary rPFS analysis. The goals of these SAs were to confirm the clinical relevance of the PCWG2 rPFS definition, to further examine concordance between central and investigator assessment using the bone capture data assay form, and to examine the correlation between rPFS and OS.

Methods

The PREVAIL study design has previously been described,[7] and the trial protocol is available in Supplement 1. This study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee at each participating center. All patients provided written informed consent before enrollment.

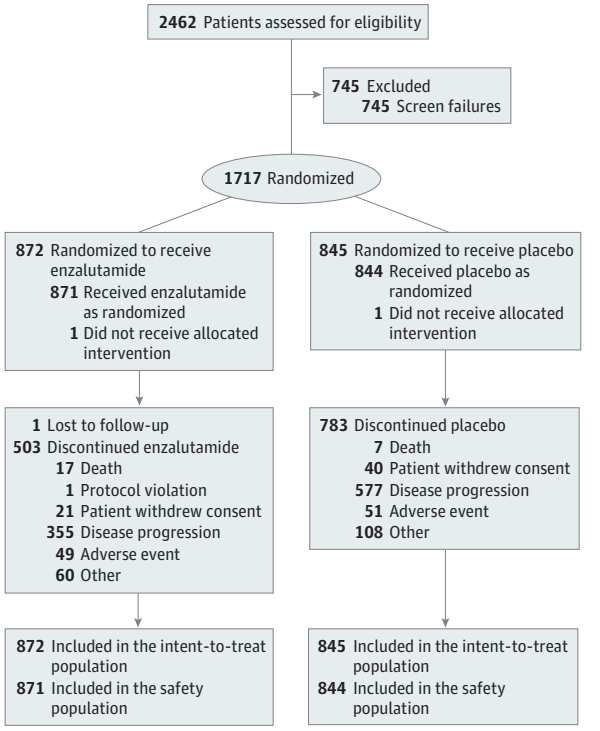
Randomization and Masking

Patients were assigned 1:1 to receive enzalutamide 160 mg or placebo using a centrally administered, randomized permuted-block method and stratified by study site. All patients, investigators, site personnel, and sponsor personnel involved in the conduct of the study were blinded to treatment assignment.

Primary Assessment of rPFS

The co-primary end points of PREVAIL were OS and rPFS, in which rPFS was defined as the time from randomization to first objective evidence of radiographic disease progression assessed by blinded independent central review or death from any cause within 168 days after treatment discontinuation, whichever occurred first. Radiographic disease progression was evaluated using a modified form of the PCWG2 guidelines for bone disease[9] and Response Evaluation Criteria in Solid Tumors, version 1.1, for soft-tissue disease.[14]

Figure 1. CONSORT Diagram



A separate investigator assessment of imaging was performed at each site using a bone scan worksheet adapted from the Prostate Cancer Clinical Trials Consortium.[11] As specified, progression in bone (≥2 new lesions on radionuclide bone scan) observed at week 9 necessitated 2 or more additional new lesions on a confirmatory scan at least 6 weeks later; radiographic disease progression in bone observed after week 9 necessitated 2 or more new lesions relative to the week 9 scan, confirmed on a subsequent scan at least 6 weeks later. Radiographic disease progression in soft tissue did not require a confirmatory scan.[14]

Sensitivity Analysis of rPFS

Six SAs (SA1-SA6) based on investigator assessments were performed (eTable 1 in Supplement 2).

Statistical Analysis and Censoring Procedures

The final intention-to-treat analysis of rPFS was performed by the independent central review facility after 439 events (data cutoff, May 6, 2012), and the interim intention-to-treat OS analysis was performed after 540 events (data cutoff, September 16, 2013).

In all analyses, patients who were not known to have had an rPFS event at the time of data cutoff were censored at the date of last assessment. In the primary analysis, SA1, and SA2, patients were censored for rPFS if, prior to objective evidence of disease progression, there was a change in tumor scan modality, initiation of a new antineoplastic treatment and/or radiation therapy for prostate cancer, SRE, treatment discontinuation, 2 or more consecutive missed tumor assessments, or death after 168 days following treatment discontinuation without progression. In SA4, patients who discontinued study drug primarily because of clinical progression before objective evidence of radiographic disease progression were considered to have clinical progression on the date of the last dose of study drug. In SA5, patients with soft-tissue disease progression through week 13 without a confirmatory scan were censored at the date of earliest soft-tissue disease progression prior to week 13. In SA3 and SA6, the same censoring rules for the primary analysis applied, except that new SREs, any radiation therapy for prostate cancer, or new antineoplastic therapy (SA3) and all deaths (SA6) were considered rPFS events.

All data analyses were performed using SAS, version 9.1.3 (SAS Institute), as previously described.[7] Estimates of medians and 95% CIs were determined using the Kaplan-Meier method. Hazard ratio relative to placebo (with less than 1.00 favoring enzalutamide) was determined using an unstratified Cox regression model with treatment as the only covariate. The analysis of rPFS was conducted using a 2-sided unstratified log-rank test with a type 1 error rate of .001.

Overall concordance between independent central review and investigator assessments (using SA1) of the intention-to-treat population was calculated as (concordance for progressive disease) + (concordance for nonprogressive disease). In addition, correlations between rPFS (using SA2) and OS were calculated using 2 methods: Spearman ρ and Kendall τ via Clayton copula.[15-18]

Results

Patient Disposition and Demographic and Clinical Characteristics

The primary results of PREVAIL have been published previously and showed that patient demographic and disease characteristics were similar between treatment arms at baseline.[7] The mean age at baseline was 72.0 (range, 43.0-93.0) years in the enzalutamide arm and 71.0 (range, 42.0-93.0) years in the placebo arm.[7] Patient disposition is presented in **Figure 1**. In all SAs presented here (except SA2), analyses were based on data from 832 patients in the enzalutamide arm and 801 patients in the placebo arm. In SA2, data from all randomized patients were used in the analysis (enzalutamide arm, n = 872; placebo arm, n = 845). Results from all analyses are presented in **Table 1**.

Primary Analysis of rPFS

At the final cutoff date for primary rPFS analysis, 118 of 832 patients (14.2%) in the enzalutamide arm had an rPFS event, compared with 321 of 801 patients (40.1%) in the placebo arm. The majority of rPFS events resulted from radiographic progression (105 of 118 and 295 of 321 patients, respectively). Thirteen of 832 patients (1.6%) in the enzalutamide arm and 26 of 801 patients (3.2%) in the placebo arm died without radiographic progression. Enzalutamide reduced the risk of radiographic progression or death by 81% compared with placebo (HR, 0.19; 95% CI, 0.15-0.23; $P < .001$).[7] Median time to an rPFS event was not reached (95% CI, 13.8 to not reached

Table 1. Summary of Radiographic Progression-Free Survival (rPFS) Sensitivity Analyses (SAs) (Intention-to-Treat Population)

Sensitivity Analysis[a]	No. (%) Enzalutamide (n = 832)	No. (%) Placebo (n = 801)	HR (95% CI)
Primary			
Total events[b]	118 (14.2)	321 (40.1)	0.19 (0.15-0.23)
Radiographic progression	105 (12.6)	295 (36.8)	
Death[c]	13 (1.6)	26 (3.2)	
SA1			
Total events[b]	117 (14.1)	296 (37.0)	0.22 (0.18-0.27)
Radiographic progression	102 (12.3)	271 (33.8)	
Death[c]	15 (1.8)	25 (3.1)	
SA2			
Total events[b,d]	387 (44.4)	502 (59.4)	0.31 (0.27-0.35)
Radiographic progression	343 (39.3)	459 (54.3)	
Death[c]	44 (5.0)	43 (5.1)	
SA3			
Total events[b]	161 (19.4)	409 (51.1)	0.21 (0.18-0.26)
Radiographic progression	94 (11.3)	219 (27.3)	
Death[c]	9 (1.1)	24 (3.0)	
Initiated antineoplastic therapy	13 (1.6)	87 (10.9)	
Initiated radiation therapy	2 (0.2)	5 (0.6)	
SRE	15 (1.8)	21 (2.6)	
SRE, initiated antineoplastic therapy	2 (0.2)	6 (0.7)	
SRE, initiated radiation therapy	26 (3.1)	47 (5.9)	
SA4			
Total events[b]	120 (14.4)	299 (37.3)	0.21 (0.17-0.26)
Clinical progression	17 (2.0)	67 (8.4)	
Radiographic progression	92 (11.1)	205 (25.6)	
Death[c]	11 (1.3)	27 (3.4)	
SA5			
Total events[b]	108 (13.0)	245 (30.6)	0.23 (0.19-0.30)
Radiographic progression	92 (11.1)	205 (25.6)	
Death[c]	16 (1.9)	40 (5.0)	
SA6			
Total events[b]	111 (13.3)	252 (31.5)	0.23 (0.19-0.30)
Radiographic progression	92 (11.1)	205 (25.6)	
Death	19 (2.3)	47 (5.9)	

Abbreviations: HR, hazard ratio; SRE, skeletal-related event.

[a] SA1 was based on investigator's assessments using final rPFS cutoff; SA2, investigator's assessments using interim overall survival cutoff; SA3, SRE, initiation of radiation therapy, and new antineoplastic therapy; SA4, clinical progression; SA5, confirmatory scan requirement for progressive disease related to soft-tissue disease; and SA6, all deaths.

[b] Based on the earliest contributing event (eTable 1 in the Supplement).

[c] Deaths only counted as rPFS events if they occurred within 168 d of treatment discontinuation and in the absence of radiographic progression.

[d] Includes all randomized patients (n = 872 for enzalutamide; n = 845 for placebo).

[NR]) in the enzalutamide arm and was 3.9 months (95% CI, 3.7-5.4 months) in the placebo arm (**Figure 2**A).[7]

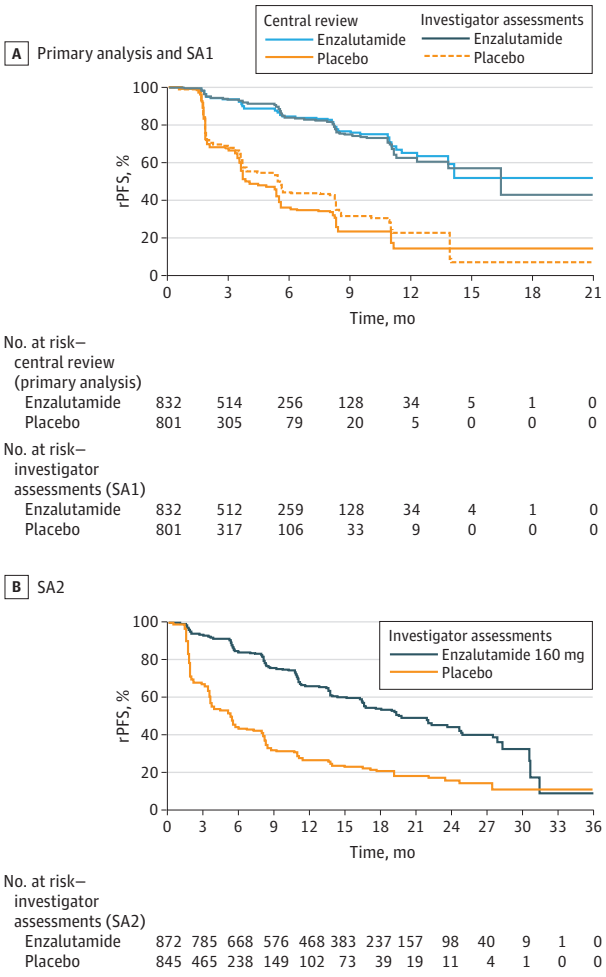
Concordance Between Independent and Investigator Assessments of rPFS

Using the same censoring rules and final rPFS data cutoff date, there was a high level of agreement between investigator assessments of radiographic progression (SA1) and those obtained by independent central assessment (eTable 2 in Supplement 2). Agreement at the final rPFS analysis between independent and investigator assessments for progressive and nonprogressive disease was 87.6% (90.9% with enzalutamide and 84.0% with placebo). Results from the remaining SAs were consistent between investigator assessment and central review (eTable 3 in Supplement 2). The main difference in investigator and central assessment for the subset analyses was the identification of soft-tissue progression, which did not use a standardized data capture form and was consistently higher when assessed by central review (eTable 4 in Supplement 2).

Sensitivity Analyses of rPFS

To remove the confounding factor of investigator assessment vs independent central review, and because SA1 differed from the primary analysis only in the use of investigator assessment, we used SA1 as the comparator. In SA1, enzalutamide treatment reduced the risk of radiographic progression or death by 78% compared with placebo (HR, 0.22; 95% CI, 0.18-0.27; $P < .001$) (Table 1). Median time to an rPFS event was 16.4 months (95% CI, 13.8 months to NR) in the enzalutamide arm and 5.5 months (95% CI, 5.2-5.6 months) in the placebo arm (Figure 2A).

Figure 2. Duration of Radiographic Progression-Free Survival (rPFS) in Primary Analysis, Sensitivity Analysis 1 (SA1), and SA2



A, Primary analysis and SA1 (intention-to-treat population, data cutoff May 6, 2012). B, SA2 (intention-to-treat population, data cutoff September 16, 2013).

SA2 included all randomized patients with an additional 16 months of data collection. As expected, the number of qualifying events increased substantially (Table 1). Enzalutamide therapy reduced the risk of radiographic progression or death by 69% (HR, 0.31; 95% CI, 0.27-0.35; $P < .001$). Median time to an rPFS event was 19.7 months (95% CI, 18.1-22.3 months) in the enzalutamide arm and 5.4 months (95% CI, 4.2-5.6 months) in the placebo arm (Figure 2B).

In SA3, in which SREs or any use of radiation or antineoplastic therapy were counted as rPFS events, there was an increase in the number of events, particularly in the placebo arm (Table 1). In both treatment arms, rPFS resulting from death decreased, whereas the bulk of the additional rPFS events were associated with new SREs and/or initiation of new antineoplastic therapies. Enzalutamide reduced the risk of radiographic progression or death by 79% (HR, 0.21; 95% CI, 0.18-0.26; $P < .001$). Median time to an rPFS event was 13.3 months (95% CI, 11.2-16.4 months) in the enzalutamide arm and 3.7 months (95% CI, 3.6-4.4 months) in the placebo arm (**Figure 3**A).

In SA4, in which rPFS events included discontinuation of treatment resulting from clinical progression prior to objective evidence of radiographic disease progression, there was a modest increase in the number of qualifying events in both treatment arms (Table 1). Enzalutamide therapy reduced the risk of radiographic progression or death by 79% (HR, 0.21; 95% CI, 0.17-0.26; $P < .001$). Median time to an rPFS event was 14.2 months (95% CI, 13.8 months to NR) in the enzalutamide arm and 5.4 months (95% CI, 4.6-5.6 months) in the placebo arm (Figure 3B).

In SA5, in which progression related to soft-tissue disease required a confirmatory scan, there was a decrease in the number of qualifying events in both treatment arms. Although the number of radiographic progression events decreased in both treatment arms, the number of deaths remained the same in the enzalutamide arm and increased in the placebo arm (Table 1). Enzalutamide treatment reduced the risk of radiographic progression or death by 77% (HR, 0.23; 95% CI, 0.19-0.30; $P < .001$). The median time to an rPFS event was 16.4 months (95% CI, 13.8 months to NR) in the enzalutamide arm and 5.7 months (95% CI, 5.5-8.2 months) in the placebo arm (Figure 3C).

The definition of rPFS in the primary analysis included death from any cause within 168 days of treatment discontinuation. In SA6, any death was considered an rPFS event, regardless of length of time after study drug discontinuation, which resulted in a modest decrease in the number of qualifying events in both treatment arms (Table 1). The number of radiographic progression events decreased in both treatment arms. As expected, the number of deaths increased in both treatment arms, although the increase was modest in the enzalutamide arm. Enzalutamide therapy reduced the risk of radiographic progression or death by 77% (HR, 0.23; 95% CI, 0.19-0.30; $P < .001$). Median time to an rPFS event was 15.0 months (95% CI, 13.8 months to NR) in the enzalutamide arm and 6.0 months (95% CI, 5.5-8.2 months) in the placebo arm (Figure 3D).

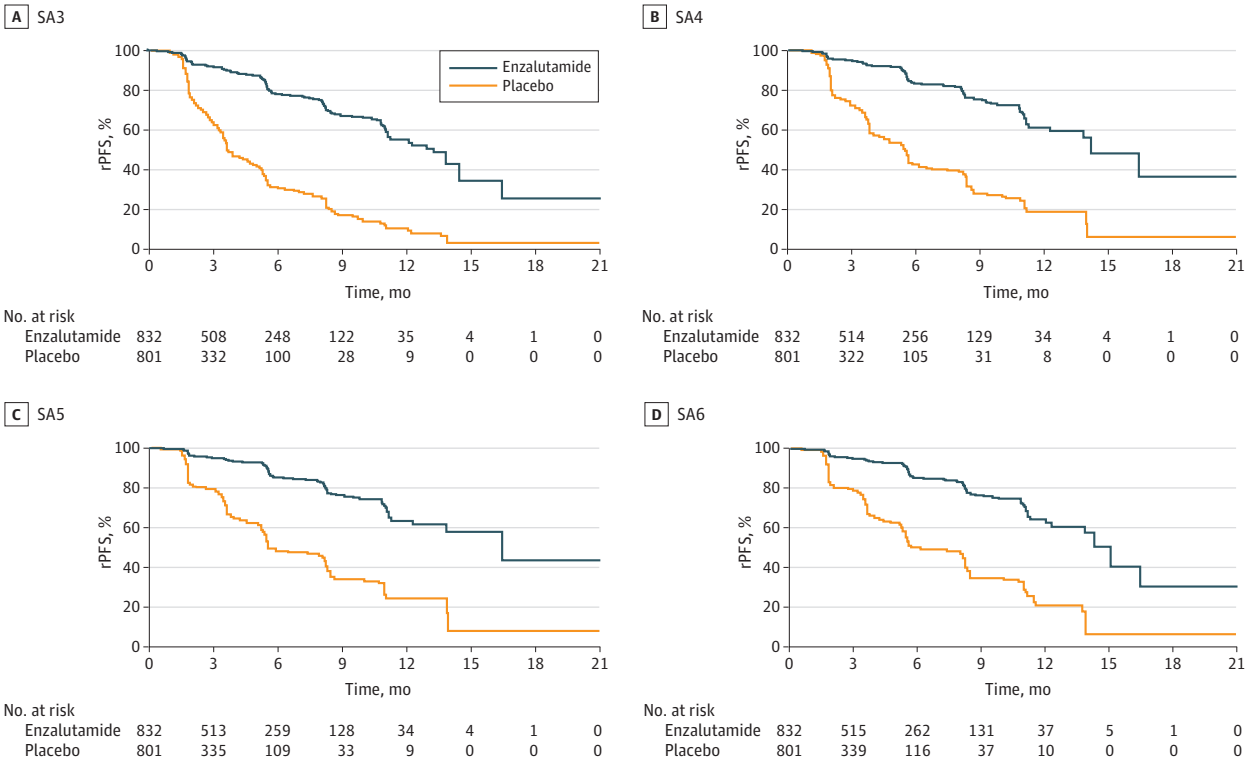
Correlation of rPFS and OS

At the planned interim analysis for OS, there were 540 deaths and 889 investigator-assessed rPFS events. Treatment with enzalutamide resulted in a 29% decrease in the risk of death compared with placebo (HR, 0.71; 95% CI, 0.60-0.84; $P < .001$).[7] Using SA2, rPFS was positively associated with OS among all patients and patients in each treatment arm using 2 different methods (**Table 2**). Spearman ρ was 0.72 (95% CI, 0.67-0.76) among all patients, 0.89 (95% CI, 0.86-0.92) among enzalutamide-treated patients, and 0.53 (95% CI, 0.43-0.61) among placebo-treated patients. Kendall τ was 0.53 (95% CI, 0.49-0.57) among all patients, 0.72 (95% CI, 0.68-0.77) among enzalutamide-treated patients, and 0.37 (95% CI, 0.30-0.44) among placebo-treated patients.

Discussion

As more life-prolonging drugs are approved for the treatment of mCRPC, addressing the need for outcome measures that strongly correlate with survival or reflect clinical benefit in their

Figure 3. Duration of Radiographic Progression-Free Survival (rPFS) in Sensitivity Analysis 3 (SA3), SA4, SA5, and SA6



All intention-to-treat population; data cutoff, May 6, 2012.

Table 2. Correlation of Radiographic Progression-Free Survival With Overall Survival[a]

Method	Correlation (95% CI)		
	Total (N = 1717)	Enzalutamide (n = 872)	Placebo (n = 845)
Spearman ρ	0.72 (0.67-0.76)	0.89 (0.86-0.92)	0.53 (0.43-0.61)
Kendall τ	0.53 (0.49-0.57)	0.72 (0.68-0.77)	0.37 (0.30-0.44)

[a] The analysis data cutoff was September 16, 2013.

own right is essential to ensure the timely development of drugs needed to further improve patient outcomes. Toward this objective, PREVAIL included in its design the co-primary end points of OS and rPFS.

The results of PREVAIL further confirmed the rigor of the PCWG2 definition of rPFS using a standardized bone scan data capture assay in patients with mCRPC. There was a high degree of concordance between the central and investigator reviews in both treatment arms. Notably, individual investigators were trained at each site using the bone scan data capture forms and the end result was a high level of reproducibility between readers, which highlights the clinical utility of this end point. The prespecified SAs in the PREVAIL study showed the impact of different clinical factors on rPFS, including SREs, initiation of radiotherapy and/or new antineoplastic therapy, and unequivocal clinical progression, which all confirmed the superiority of enzalutamide over placebo.

The PREVAIL analysis is the second to demonstrate a positive correlation between rPFS using the PCWG2 criteria and OS (Spearman ρ of 0.72 and Kendall τ of 0.53 for all patients). The COU-AA-302 trial also demonstrated a correlation between rPFS and OS[12]; both studies used the PCWG2 definition of radiographic progression, involved patients with mCRPC who had not received chemotherapy, and involved treatment that targeted the AR axis. Both studies also found a high concordance between the central and investigator reads, validating the reproducibility of the analytically validated bone scan progression biomarker to document rPFS disease progression. Notably, there were only 188 progression events in the PREVAIL enzalutamide arm vs 542 in the COU-AA-302 abiraterone acetate plus prednisone arm. As a result, although the HR was high for the enzalutamide arm (0.19), the event rate was relatively low, a fact that may bias the analyses accordingly.

Because the distribution of data was not known up front, 2 different statistical methods were used that measured correlation in slightly different ways. Spearman ρ and Kendall τ rank correlations are both nonparametric tests, with no assumption about the distribution of data and often used for nonlinear monotonic relationships.[19] Spearman ρ measures how the magnitude and direction of change of one end point

corresponds to the magnitude and direction of change of the other end point, whereas Kendall τ only considers the direction of change. Consequently, Kendall τ generally results in a value closer to 0 (no correlation) than Spearman ρ does.[20] Results from both analyses in this study were consistent, with a positive correlation.

In our analysis, the lower correlation between rPFS and OS seen with placebo-treated patients than seen with enzalutamide-treated patients could be partly related to postprotocol exposure to life-prolonging therapy. Patients in the placebo arm received more postprotocol therapies than those in the enzalutamide arm (76% vs 44%), including docetaxel (57% vs 33%), abiraterone acetate (46% vs 21%), and enzalutamide (4% vs 1%).[7]

Limitations

PREVAIL and COU-AA-302 both studied drugs that target the AR signaling pathway and enrolled chemotherapy-naive patients with mCRPC. The use of a co-primary end point using both OS and rPFS in both studies was designed to clearly demonstrate clinical benefit; however, the studies were not designed to address rPFS as a surrogate for survival. In addition, the results based on end points from these AR-directed trials may not be applicable to biologic agents, bone microenvironment-directed approaches, and non-AR-targeted therapies, whose impact on the tumor, and consequently on radiographic progression, has not yet been fully defined. It is anticipated that a one-size-fits-all end point that is general enough to encompass all therapies in all clinical scenarios will not be sufficient to enable regulatory approvals. As a result, the definition of rPFS as a clinically relevant end point may need to be adapted and, if so, revalidated accordingly to fit the disease, population, imaging modality, and treatment involved.

Conclusions

In this series of prespecified SAs of data from the PREVAIL trial of men with chemotherapy-naive mCRPC, the PCWG2 definition of rPFS was found to be a robust and clinically meaningful end point associated with OS in enzalutamide-treated patients.

ARTICLE INFORMATION

Accepted for Publication: December 13, 2017.

Published Online: March 8, 2018. doi:10.1001/jamaoncol.2017.5808

Author Affiliations: Genitourinary Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center and Weill Cornell Medicine, New York, New York (Rathkopf, Scher, Morris); Department of Hematology/Medical Oncology, OHSU Knight Cancer Institute, Oregon Health and Science University, Portland (Beer); Gustave Roussy, Cancer Campus, Department of Cancer Medicine, University of Paris Saclay, Villejuif, France (Loriot); Department of Medical Oncology, University of Washington and Fred Hutchinson Cancer Research Center, Seattle, Washington (Higano); Divisions of Medical Oncology and Urology, Duke University Medical Center, Duke Cancer Institute, Duke University, Durham, North Carolina (Armstrong); Department of Medical Oncology, San Camillo and Forlanini Hospitals, Rome, Italy (Sternberg); Division of Clinical Studies, Royal Marsden Hospital and Institute of Cancer Research, London, England (de Bono); Division of Urology, Cliniques Universitaires Saint-Luc, Brussels, Belgium (Tombal); Department of Clinical Development, Medivation, LLC, a Pfizer company, San Francisco, California (Parli); formerly with Department of Biostatistics, Medivation, LLC, a Pfizer company, San Francisco, California (Bhattacharya); Department of Biostatistics, Astellas Pharma Europe BV, Leiden, The Netherlands (Phung); Department of Medical Oncology, Astellas Pharma, Inc, Northbrook, Illinois (Krivoshik).

Author Contributions: Dr Morris had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Rathkopf, Beer, Armstrong, Sternberg, de Bono, Tombal, Bhattacharya, Phung, Krivoshik, Scher, Morris.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Rathkopf, Armstrong, Sternberg, de Bono, Bhattacharya, Phung, Krivoshik, Morris.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Bhattacharya, Phung.
Administrative, technical, or material support: Loriot, Armstrong, de Bono, Scher, Morris.
Study supervision: Rathkopf, Beer, Armstrong, Sternberg, de Bono, Tombal, Bhattacharya, Krivoshik, Scher, Morris.

Conflict of Interest Disclosures: Dr Rathkopf has received advisory/consulting fees from Janssen and research funding for her institution from AstraZeneca, Astellas Pharma, Celgene, Genentech, Janssen, Medivation, Millenium, Novartis, Pfizer, Roche, and Tracon. Dr Beer owns stock in Salarius Pharma. He has received consulting/advisory fees from AstraZeneca, Churchill Pharma, Dendreon, Janssen Biotech, Janssen Japan, Janssen Oncology, Janssen R&D, and Johnson & Johnson. His institution has received research funding from Astellas Pharma, Boehringer Ingelheim, Bristol-Myers Squibb, Dendreon, Janssen R&D, Medivation, OncoGenex, Sotio, and Theraclone Sciences. Dr Loriot has received consulting fees and nonfinancial support from Astellas Pharma, Bristol-Myers Squibb, MSD, Pfizer, and Roche. He has received research funding, consulting fees, and nonfinancial support from Sanofi. He has received consulting fees from AstraZeneca. Dr Higano has received consulting/advisory fees from Aptevo, Asana, Astellas Pharma, Bayer, Blue Earth Diagnostics, Churchill, Clovis, Dendreon, Endocyte, Ferring, Medivation, MorphoSys, Orion, and Pfizer. She has received research funding from Aptevo, Aragon, AstraZeneca, Bayer, Dendreon, Exelixis, Genentech, Medivation, Millennium, Pfizer, Sanofi, and Teva. Dr Armstrong has received consulting fees and research funding for his institution from Astellas Pharma, Bayer, Dendreon, Janssen, Medivation, Pfizer, Sanofi, and Valeant. He reports research funding to his institution from Active Biotech, Bristol-Myers Squibb, Genentech, Gilead, Novartis, and Roche. Dr Sternberg has received honoraria from Astellas Pharma, Bayer, Bristol-Myers Squibb, Eisai, GlaxoSmithKline, Ipsen, Janssen, Lilly, MSD, Novartis, Pfizer, and Sanofi. Dr de Bono has received consulting fees and nonfinancial support from Astellas Pharma, AstraZeneca, Genentech, Roche, and Sanofi. Dr Tombal has received honoraria from Amgen, Astellas Pharma, Bayer, Ferring, Janssen, and Sanofi. He has received consulting/advisory fees from Astellas Pharma, Bayer, Ferring, Janssen, Sanofi, Steba Biotech, and Takeda. He has served on speakers' bureaus for Amgen and Janssen. He has received research funding from Ferring. He has received funding for travel from Amgen, Astellas Pharma, Bayer, Ferring, Janssen, and Sanofi. Dr Parli is an employee of Medivation, LLC, a Pfizer company. Dr Bhattacharya is a former employee of Medivation, LLC, a Pfizer company. Mr Phung is an employee of Astellas Pharma. Dr Krivoshik is an employee of Astellas Pharma. He owns stock in Abbott and AbbVie. He has a patent with Abbott. Dr Scher is on the Board of Directors for Asterias Biotherapeutics. He is a compensated consultant for Astellas Pharma, BIND Pharmaceuticals, Blue Earth Diagnostics, Clovis Oncology, Med IQ, Merck, OncLive, Physicians Education Resource, Roche, Sanofi Aventis, and WIRB Copernicus Group. He is an uncompensated consultant for Ferring Pharmaceuticals, Medivation, and Pfizer. He has received research funding for his institution from Illumina, Innocrin Pharma, Janssen, and Medivation. Dr Morris is a compensated consultant for Advanced Accelerator Applications. He is an uncompensated consultant for Astellas Pharma, Bayer, Endocyte, Progenics, and Tokai. He has received research funding for his institution from Bayer, Progenics, and Endocyte. No other disclosures are reported.

Funding/Support: The PREVAIL trial and analyses presented in this article were sponsored by Pfizer Inc and Astellas Pharma, Inc. Drs Rathkopf, Scher, and Morris also received support through the National Institutes of Health/National Cancer Institute Cancer Center Support Grant P30 CA008748.

Role of the Funder/Sponsor: Authors who are employed by the study sponsors Medivation, LLC, a Pfizer company, and Astellas Pharma, Inc, were involved in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation of the manuscript; and the decision to submit the manuscript for publication.

Additional Contributions: Glen Heller, PhD, Memorial Sloan Kettering, and Kenneth Wu, PhD, formerly of Medivation, LLC, a Pfizer company, provided assistance with the correlation analyses. Medical writing and editorial support, funded by Medivation, LLC, a Pfizer company, and Astellas Pharma, Inc, was provided by Stephanie Vadasz, PhD, Shannon Davis, and Joshua Safran, of Ashfield Healthcare Communications.

REFERENCES

1. de Bono JS, Oudard S, Ozguroglu M, et al; TROPIC Investigators. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet*. 2010;376(9747):1147-1154.

2. de Bono JS, Logothetis CJ, Molina A, et al; COU-AA-301 Investigators. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med*. 2011;364(21):1995-2005.

3. Kantoff PW, Higano CS, Shore ND, et al; IMPACT Study Investigators. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med*. 2010;363(5):411-422.

4. Scher HI, Fizazi K, Saad F, et al; AFFIRM Investigators. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med*. 2012;367(13):1187-1197.

5. Ryan CJ, Smith MR, de Bono JS, et al; COU-AA-302 Investigators. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med*. 2013;368(2):138-148.

6. Parker C, Nilsson S, Heinrich D, et al; ALSYMPCA Investigators. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med*. 2013;369(3):213-223.

7. Beer TM, Armstrong AJ, Rathkopf DE, et al; PREVAIL Investigators. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med*. 2014;371(5):424-433.

8. Ryan CJ, Smith MR, Fizazi K, et al; COU-AA-302 Investigators. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol*. 2015;16(2):152-160.

9. Scher HI, Halabi S, Tannock I, et al; Prostate Cancer Clinical Trials Working Group. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol*. 2008;26(7):1148-1159.

10. Ryan CJ, Shah S, Efstathiou E, et al. Phase II study of abiraterone acetate in chemotherapy-naive metastatic castration-resistant prostate cancer displaying bone flare discordant with serologic response. *Clin Cancer Res*. 2011;17(14):4854-4861.

11. Morris MJ, Farrelly JS, Fox JJ, Dennis ER, Schwartz LH, Schoder H. The Prostate Cancer Clinical Trials Consortium (PCCTC) bone scan data capture tool for clinical trials using Prostate Cancer Working Group 2 (PCWG2) criteria: effect on data accuracy and workload. *J Clin Oncol*. 2011;29(7 suppl):121.

12. Morris MJ, Molina A, Small EJ, et al. Radiographic progression-free survival as a response biomarker in metastatic castration-resistant prostate cancer: COU-AA-302 results. *J Clin Oncol*. 2015;33(12):1356-1363.

13. Bhattacharya S, Fyfe G, Gray RJ, Sargent DJ. Role of sensitivity analyses in assessing progression-free survival in late-stage oncology trials. *J Clin Oncol*. 2009;27(35):5958-5964.

14. Eisenhauer EA, Therasse P, Bogaerts J, et al. New Response Evaluation Criteria in Solid Tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247.

15. Oakes D. On consistency of Kendall's tau under censoring. *Biometrika*. 2008;95(4):997-1001.

16. Multivariate dependence with copulas. 2017. https://cran.r-project.org/web/packages/copula/copula.pdf. Accessed November 27, 2017.

17. Nelsen RB. *An Introduction to Copulas*. New York, NY: Springer-Verlag; 2006.

18. Nelsen RB. Properties and applications of copulas: a brief survey. In: *Proceedings of the First Brazilian Conference on Statistical Modeling in Insurance and Finance*. São Paulo, Brazil: University of São Paulo Press; 2003:10-28.

19. Correlation (Pearson, Kendall, Spearman). Statistics Solutions website. http://www.statisticssolutions.com/correlation-pearson-kendall-spearman/. Accessed March 8, 2016.

20. Kendall's tau and Spearman's rank correlation coefficient. Statistics Solutions website. https://www.statisticssolutions.com/kendalls-tau-and-spearmans-rank-correlation-coefficient/. Accessed March 11, 2016.

special article

Evolving Intersection Between Inherited Cancer Genetics and Therapeutic Clinical Trials in Prostate Cancer: A White Paper From the Germline Genetics Working Group of the Prostate Cancer Clinical Trials Consortium

Maria I. Carlo
Veda N. Giri
Channing J. Paller
Wassim Abida
Joshi J. Alumkal
Tomasz M. Beer
Himisha Beltran
Daniel J. George
Elisabeth I. Heath
Celestia S. Higano
Rana R. McKay
Alicia K. Morgans
Akash Patnaik
Charles J. Ryan
Edward M. Schaeffer
Walter M. Stadler
Mary-Ellen Taplin
Noah D. Kauff
Jacob Vinson
Emmanuel S. Antonarakis
Heather H. Cheng

Author affiliations and support information (if applicable) appear at the end of this article.

Opinions, interpretations, conclusions and

(continued)

executive summary

Purpose Advances in germline genetics, and related therapeutic opportunities, present new opportunities and challenges in prostate cancer. The Prostate Cancer Clinical Trials Consortium Germline Genetics Working Group was established to address genetic testing for men with prostate cancer, especially those with advanced disease undergoing testing for treatment-related objectives and clinical trials.

Methods The Prostate Cancer Clinical Trials Consortium Germline Genetics Working Group met monthly to discuss the current state of genetic testing of men with prostate cancer for therapeutic or clinical trial purposes. We assessed current institutional practices, developed a framework to address unique challenges in this population, and identified areas of future research.

Results Genetic testing practices in men with prostate cancer vary across institutions; however, there were several areas of agreement. The group recognized the clinical benefits of expanding germline genetic testing, beyond cancer risk assessment, for the goal of treatment selection or clinical trial eligibility determination. Genetic testing for treatment selection should ensure patients receive appropriate pretest education and consent and occur under auspices of a research study whenever feasible. Providers offering genetic testing should be able to interpret results and recommend post-test genetic counseling for patients. When performing tumor (somatic) genomic profiling, providers should discuss the potential for uncovering germline mutations and recommend appropriate genetic counseling. In addition, family members may benefit from cascade testing and early cancer screening and prevention strategies.

Conclusion As germline genetic testing is incorporated into practice, further development is needed in establishing prompt testing for time-sensitive treatment decisions, integrating cascade testing for family, ensuring equitable access to testing, and elucidating the role of less-characterized germline DNA damage repair genes, individual gene-level biologic consequences, and treatment response prediction in advanced disease.

JCO Precis Oncol.

recommendations are those of the author and are not necessarily endorsed by the Department of Defense.

Corresponding author: Heather H. Cheng, MD, PhD, Division of Medical Oncology, University of Washington, 825 Eastlake Ave E, Seattle, WA 98109; e-mail: hhcheng@uw.edu.

INTRODUCTION

Although the contribution of heredity to prostate cancer has long been known, the underlying genetic causes remained elusive. Recent discoveries reveal that a significant fraction of men with metastatic prostate cancer (mPC) carry germline mutations in DNA damage repair (DDR) genes, including *BRCA1*, *BRCA2*, and *ATM*.[1,2] Compelling early findings suggest that germline and/or somatic alterations in these and other DDR genes may predict response to poly (ADP-ribose) polymerase (PARP) inhibitors and platinum chemotherapy.[3-5] Germline mutations in mismatch repair (MMR) genes (*MSH2*, *MSH6*, *MLH1*, and *PMS2*), which are associated with Lynch syndrome and development of tumors with defective DNA MMR or high microsatellite instability (MSI), may identify candidates for immunotherapy with programmed cell death protein 1 checkpoint inhibitors.[6] In addition, response to other systemic therapies for prostate cancer may be influenced by the presence of a germline and/or somatic DDR gene mutation.[7-10]

Table 1. Selected Therapeutic Clinical Trials in Prostate Cancer With Relevance to Germline Genetics

Phase	Title	Disease State	Abbreviated Title	ClinicalTrials.gov Identifier
III	Study of Olaparib Versus Enzalutamide or Abiraterone Acetate in Men With Metastatic Castration-Resistant Prostate Cancer (PROfound Study)	mCRPC	PROfound	NCT02987543
III	A Study of Rucaparib Verses Physician's Choice of Therapy in Patients With Metastatic Castration-Resistant Prostate Cancer and Homologous Recombination Gene Deficiency (TRITON3)	mCRPC	TRITON3	NCT02975934
II	A Phase 2 Efficacy and Safety Study of Niraparib in Men with Metastatic Castration-Resistant Prostate Cancer and DNA-Repair Anomalies	mCRPC	GALAHAD	NCT02854436
II	A Multicenter, Open-Label Phase 2 Study of Rucaparib in Patients With Metastatic Castration-Resistant Prostate Cancer Associated With Homologous Recombination Deficiency	mCRPC	TRITON2	NCT02952534
II	Response Rate Study of Talazoparib in Men With DNA Repair Defects and Metastatic Castration-Resistant Prostate Cancer Who Previously Received Taxane-Based Chemotherapy and Progressed on at Least 1 Novel Hormonal Agent (Enzalutamide and/or Abiraterone Acetate/Prednisone)	mCRPC		NCT03148795
II	Olaparib in Men With High-Risk Biochemically-Recurrent Prostate Cancer Following Radical Prostatectomy, With Integrated Biomarker Analysis	BCR		NCT03047135
II	Abiraterone/Prednisone, Olaparib, or Abiraterone/Prednisone + Olaparib in Patients With Metastatic Castration-Resistant Prostate Cancer With DNA Repair Defects	mCRPC	BRCAaway	NCT03012321
I	A Safety and Pharmacokinetics Study of Niraparib Plus an Androgen Receptor-Targeted Therapy in Men With Metastatic Castration-Resistant Prostate Cancer (BEDIVERE)	mCRPC	BEDIVERE	NCT02924766
Pilot	Docetaxel and Carboplatin in Treating Patients With Metastatic, Hormone Resistant Prostate Cancer Containing Inactivated Genes in the BRCA 1/2 Pathway	mCRPC	ABCD	NCT02598895
II	The BARCODE 2 Study—The Use of Genetic Profiling to Guide Prostate Cancer Treatment (BARCODE2)	mCRPC	BARCODE-2	NCT02955082
II	Docetaxel and Carboplatin for Patients With mCRPC and DNA-Repair Deficiencies	mCRPC	V-ABCD	NCT02985021
II	Pembrolizumab in Treating Patients With Metastatic Castration Resistant Prostate Cancer Previously Treated With Enzalutamide	mCRPC		NCT02312557
II	Study of Pembrolizumab (MK-3475) in Participants With Metastatic Castration-Resistant Prostate Cancer	mCRPC	KEYNOTE-199	NCT02787005
Ib/II	Study of Pembrolizumab (MK-3475) Combination Therapies in Metastatic Castration-Resistant Prostate Cancer	mCRPC	KEYNOTE-365	NCT02861573

Abbreviations: BCR, biochemical recurrence; mCRPC, metastatic castration-resistant prostate cancer.

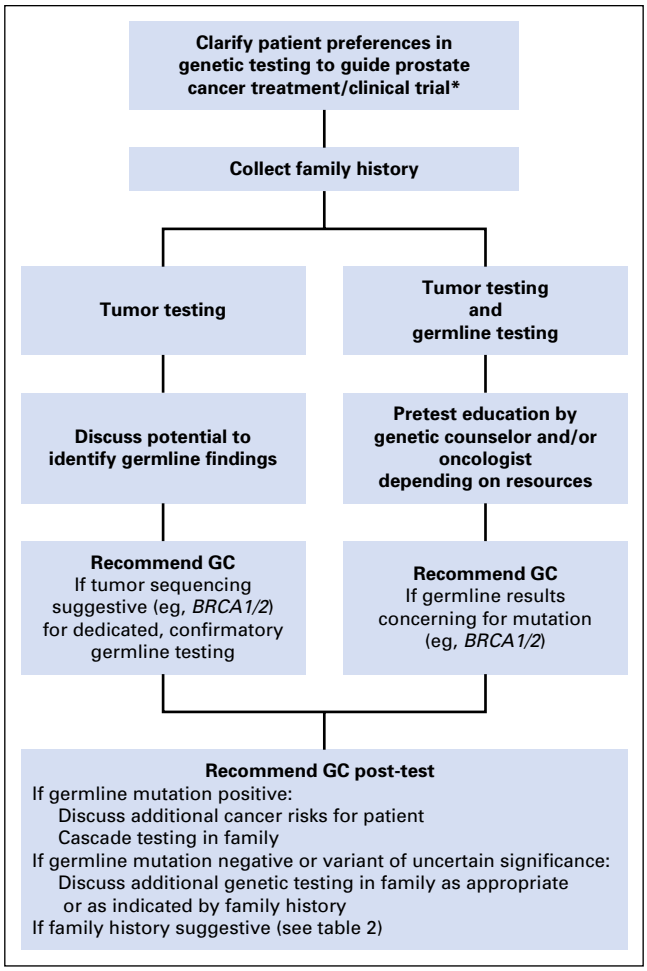


Fig 1. Framework for approaching genetic testing within the context of therapeutic decisions. (*) Currently primarily relevant to metastatic and high-risk localized prostate cancer, but likely will include earlier disease states in the future. GC, genetic counseling.

The current models for genetic counseling and testing were developed for assessment of individuals and families with suspicion for hereditary cancer syndromes and focused on risk assessment, cancer screening, and risk reduction (eg, salpingo-oophorectomy for female *BRCA1/2* carriers). For prostate cancer, genetic counseling and testing practices are newly driven by a growing interest in identifying patients who are candidates for enrollment in biomarker-selected clinical trials. This treatment-driven ascertainment, where patients are referred for germline testing in part for therapy selection, presents unique opportunities and challenges for practitioners regarding appropriate delivery of elements of genetic counseling in a feasible manner.

The Prostate Cancer Clinical Trials Consortium is a group of researchers from 11 institutions working together to develop novel therapeutics and biomarkers, translating scientific discoveries to improve standards of care in prostate cancer. The Germline Genetics Working Group of the Prostate Cancer Clinical Trials Consortium was established in June of 2017 in response to the growing intersection between germline genetics and therapeutics. In this article, we outline the special considerations when genetic testing is used for therapeutic purposes in men with mPC and to suggest areas of future research. Although germline genetics may affect management decisions in early-stage prostate cancer, we focus here on advanced disease because of the current therapeutic and clinical trial implications, although many of the principles outlined apply to all stages of disease.

GERMLINE DNA REPAIR MUTATIONS IN RECURRENT AND METASTATIC PROSTATE CANCER

Prostate cancer has a significant heritable component, with 57% of the risk attributed to genetic factors.[11,12] Mutations in high and moderately penetrant genes involved in DDR can be associated with varying degrees of increased predisposition to prostate cancer (Appendix

Table 2. Referral Criteria for Genetic Counseling for Men with Prostate Cancer

Criteria
Recommend genetic counseling if:
Metastatic prostate cancer (radiographic evidence or biopsy proven)
Prostate cancer Gleason score ≥ 7 AND family history:
One or more relatives with ovarian or breast cancer diagnosed at age ≤ 50 years OR
Two or more relatives on same side of family diagnosed with cancer, especially breast, ovary, pancreas, prostate (Gleason score ≥ 7), colon, endometrial
Consider genetic counseling if:
High-risk or very high-risk localized prostate cancer
Any-risk prostate cancer AND family history:
Father, brother, or multiple family members with prostate cancer age ≤ 50 years OR
Relative with breast, ovarian, or pancreas cancer OR
Relative with Lynch syndrome–related cancer (colon, endometrial, gastric, ovarian, upper tract urothelial, pancreas, bile duct)

Adapted from National Comprehensive Cancer Network guidelines (https://www.nccn.org/professionals/physician_gls/default.aspx#genetics_screening; https://www.nccn.org/professionals/physician_gls/default.aspx#genetics_colon; https://www.nccn.org/professionals/physician_gls/default.aspx#prostate).

Table A1). In a landmark study, the incidence of inherited pathogenic DDR mutations in men with mPC was 11.8% (5.3% with mutations in *BRCA2*, 1.9% in *CHEK2*, and 1.5% in *ATM*).[1] This prevalence was significantly higher compared with men with localized prostate cancer (11.8% *v* 4.6%; $P < .001$). In a second confirmatory study, the prevalence of germline pathogenic DDR mutations in unselected patients with recurrent or mPC was 14.0% (6.0% in *BRCA2*, 2.0% in *CHEK2*, and 2.0% in *ATM*), with an apparent enrichment in men with intraductal or ductal histologic features.[13] An association between germline *BRCA2* mutations and intraductal prostate cancer was also reported in a prior study.[14]

Germline *BRCA1/2* mutation carriers may have more aggressive disease at presentation and have a higher risk of recurrence and prostate cancer–specific mortality compared with noncarriers.[15-17] In a retrospective case-case study of patients with low-risk localized prostate cancer and patients who died as a result of disease, the combined carrier rate of *BRCA1*, *BRCA2*, and *ATM* mutations was higher in lethal cases (6.1% *v* 1.4%; $P < .001$), and those with mutations had a shorter interval to death after diagnosis.[18]

Men with Lynch syndrome (due to germline mutations in *MLH1*, *MSH2*, *MSH6*, or *PMS2*) may also be at increased risk of prostate cancer; however, data are conflicting, with some studies showing a two- to five-fold increased risk and others showing no increased risk.[19-23] These risk ranges may be due to the different penetrance of Lynch genes; there is suggestion that prostate cancer risk is particularly elevated in *MSH2* carriers.[24,25] It is also likely that as screening for colorectal cancer improves, men with Lynch syndrome are living longer, and thus the incidence of older-onset cancers is increasing.[25] Unfortunately, many patients with prostate cancer with germline MMR mutations do not meet traditional family history criteria.[26] In men with Lynch syndrome, prostate cancer infrequently represents the index cancer; however, prostate tumors can lack MMR gene protein expression or show MSI.[21,27] In a study of 451 patients with prostate cancer, 3% of patients had tumors with somatic alterations in MMR genes, which predicted for high mutation count.[28] Identifying patients with mPC whose tumors harbor these features has become increasingly relevant, because the programmed cell death protein 1 immune checkpoint inhibitor pembrolizumab was approved by the US Food and Drug Administration for treatment of any cancer with deficient MMR or high MSI.[29]

CLINICAL TRIALS USING GERMLINE MUTATIONS AS ELIGIBILITY CRITERIA

An increasing number of therapeutic clinical trials in prostate cancer are using presence of DDR mutations, including germline, as an eligibility requirement for enrollment, similar to advanced ovarian and breast cancers with germline *BRCA1/2* mutations (eg, olaparib, rucaparib; Table 1). For example, the BRCAaway trial (ClinicalTrials.gov identifier: NCT03012321) is a phase II randomized trial of the PARP inhibitor olaparib versus abiraterone versus the combination of the two agents in men with germline or somatic homologous recombination deficiency mutations. Additional trials are exploring the efficacy of rucaparib, niraparib, and olaparib as single agent for men with metastatic castration-resistant prostate cancer and a deleterious genomic alteration, either germline or somatic, in *BRCA2*, *BRCA1*, and other DDR genes (ClinicalTrials.gov identifiers: NCT02952534, NCT02975934, NCT02854436,NCT02987543).TheTRIUMPH (Trial of Rucaparib in Patients With Metastatic Hormone-Sensitive Prostate Cancer Harboring Germline DNA Repair Gene Mutations) trial (ClinicalTrials.gov identifier: NCT03413995) will enroll men with metastatic hormone-sensitive prostate cancer and a germline DDR gene pathogenic alteration, who will be treated with the PARP inhibitor rucaparib in the absence of hormonal therapy. It is anticipated that an increasing number of men with mPC will undergo genetic testing and that new trials will be designed and implemented for the germline DDR-deficient population.

CONTEXTUAL DIFFERENCES AND IMPORTANCE OF CONFIRMING PATIENT PRIORITIES

Next-generation sequencing has made germline testing more accessible and comprehensive, and broader cohorts of patients with cancer are being tested using large gene panels. These approaches have the potential to address two important but distinct objectives: first, treatment and clinical

Table 3. Clinical Trials Testing Novel Approaches to Genetic Testing

Title	Novel Approaches	ClinicalTrials.gov Identifier
Genetic Evaluation of Men—The GEM Registry	Prospective research registry of men with prostate cancer or at increased risk	NCT03076242
GENTleMEN: Genetic Testing for Men with Metastatic Prostate Cancer	Web-based consent and pretest counseling Web-based and phone-based post-test counseling Pathogenic and likely pathogenic mutation results are delivered by a genetic counselor over the phone and invited for in-person counseling	NCT03503097
Evaluating an Alternative Clinical Genetics Cancer Care Delivery Model: A Pilot Study of Patient Outcomes	Consenting by primary oncologist or urologist, same-day blood draw Standard pretest education and video Risk assessment and delivery of results by a genetic counselor by telephone	NCT02987543
ProGen: Genetic Counseling Processes and Outcomes Among Males with Prostate Cancer	Comparison of standard genetic counseling *v* video-based counseling with in-person counseling only for patients with germline mutations	NCT03328091

trial possibilities, and, second, inherited cancer risk. For providers, it is worth discussing and confirming patient goals before offering testing—for example, asking whether patients are interested primarily in treatment options, familial risk assessment, or both. Figure 1 provides a framework for genetic testing within the context of treatment decisions. Oncologist-driven genetic education is ideally in close collaboration with a cancer genetics service. Family history intake is critical and needs to be streamlined for oncology and clinical trial settings. Table 2 summarizes clinical criteria to consider for referral to genetic counseling.

This panel agrees that men with prostate cancer who undergo germline genetic testing for therapeutic or clinical trial options should receive pretest education on the implications of a positive result for themselves and for their families. Which genes should be included in testing may vary if the setting is treatment decision making versus risk assessment and risk management. For example, although at least *BRCA1/2* and MMR genes should be tested for men who meet criteria for the corresponding syndromes, additional genes, such as *ATM*, *CHEK2*, and *PALB2*, could be included for therapeutic decision making, especially in the clinical trial setting.[4,30,31]

TUMOR-ONLY SEQUENCING MAY IDENTIFY GERMLINE MUTATIONS

Targeted next-generation sequencing of the tumor is also increasingly being used for treatment decision making and clinical trial eligibility determination. Although the goal of testing may be to identify treatment options, there is a possibility that somatic testing may identify germline mutations that are reflected in tumor sequence. In several recent studies of research somatic sequencing, germline mutations with clinical implications were identified.[32,33] Tumor sequencing may even be more sensitive in detecting genetic syndromes, such as Lynch, than the traditional molecular tests.[34]

Most commercial tumor assays do not specifically report whether a mutation is present in the germline, and some subtract the germline component, but the presence of well-described founder mutations may be highly suggestive. For example, the Ashkenazi Jewish *BRCA1/2* founder mutations (*BRCA1* 185delAG; *BRCA1* 5382insC; *BRCA2* 6174delT) are almost always germline, not somatic, events, and ordering providers should be familiar with them. Somatic tumor profiling can also identify increased mutation load and MSI, which can be associated with germline MMR mutations (Lynch syndrome).[35]

Although it seems that most patients are interested in knowing secondary germline findings, they also expect their providers to offer decision-making guidance and clarify key information.[36,37] This panel agrees that men with prostate cancer who undergo tumor-based genetic testing for therapeutic or clinical trial options should be educated about the potential for uncovering germline mutations, which may warrant referral to a cancer genetic specialist for confirmatory germline testing. This panel recommends that if a *BRCA1* or *BRCA2* mutation is identified on

tumor-based testing, patients should be referred for discussion of dedicated, confirmatory germline testing. Moreover, if increased mutational load, a high MSI, or MMR deficiency is identified in tumor-only profiling, the patient's family history and personal history of other malignancies should be confirmed and reviewed with consideration for referral for dedicated confirmatory germline testing.

NEED FOR NEW GENETICS CARE DELIVERY MODELS

A major challenge is how best to integrate the workflow and provide the clinical support needed for responsible genetics care. The traditional clinical genetics cancer care delivery model—where patients are referred to a genetic counselor for in-person, pretest risk assessment and education and in-person post-test counseling—cannot meet the projected demand for testing of patients with prostate cancer, some facing time-sensitive treatment decisions. Even when testing is performed primarily for treatment selection, building in systems for those who are interested in testing of family members is of critical importance.

Current barriers to genetic testing have been described in the context of testing for cancer predisposition in hereditary breast and ovarian cancer and Lynch syndromes. These barriers include process issues (referral to genetic counseling and testing, access, wait times, insurance coverage); physician knowledge, comfort, and time; patients' lack of awareness and understanding; and refusal of testing. With appropriate education, patients may be more interested in pursuing testing. For example, > 85% of patients with ovarian cancer reported willingness to be tested if there were therapeutic implications or benefit to family, and a majority believed that genetic testing should be offered before or at the time of diagnosis.[38]

When testing for therapeutic decision making, the ability to undergo assessment and testing and receive results in a timely manner is of utmost

Table 4. Challenges and New Research Directions

Challenge or Direction
Defining which patients should be offered germline genetic testing and at what point(s) in the diagnosis/treatment timeline
The role of less-studied germline DNA-damage repair genes for therapeutic decision making and clinical trial eligibility
Best framework and workflows for rapid testing for time-sensitive therapeutic decisions
Integration of cascade education and testing for family members
Ensuring historically underserved populations have access to genetic testing

Table 5. Consensus Statements

Statement
General considerations when ordering germline testing
When feasible, genetic testing for therapeutic purposes should be performed in the setting of a research trial
Providers who choose to order germline testing themselves should be able to interpret test results (positive, negative, and variant of uncertain significance) and be prepared to initiate or refer for cascade testing of family members
Men diagnosed with an inherited genetic mutation should be referred for management of other associated cancer risks, and their blood relatives should be referred for cascade testing
Considerations during tumor-only genomic profiling
Men referred for tumor-only genomic profiling should be counseled on the potential for uncovering germline mutations, which may warrant referral to a genetic specialist for confirmatory germline testing
In tumor-only genomic profiling, pathogenic mutations in *BRCA1* or *BRCA2* should prompt referral for discussion of confirmatory germline testing
Men with prostate cancers with high microsatellite instability or mismatch repair deficiency or with tumor-only profiling with mutations *MSH2*, *MLH1*, *MSH6*, or *PMS2* should have an expanded family history to screen for Lynch syndrome or be considered for referral for genetic counseling
Considerations with germline testing for therapeutic purposes or clinical trial eligibility
If the purpose of testing is identifying potential therapeutic targets or determining eligibility for clinical trials, multigene panel testing (beyond *BRCA1/BRCA2*) is acceptable
If the purpose of testing is identifying potential therapeutic targets or determining eligibility for clinical trials, testing men without significant family history of prostate or other *BRCA* or Lynch syndrome–associated cancers is acceptable

importance. Newer approaches in cancer risk genetics include video- or phone-based pretest counseling and mainstreaming, an approach in which trained individuals provide standardized consenting and counseling before testing and genetics referral.[39] The ENGAGE (Evaluation of a Streamlined Oncologist-Led *BRCA* Mutation Testing and Counseling Model for Patients With Ovarian Cancer) study of oncologist-led *BRCA1/2* mutation testing in women with ovarian cancer showed that this process is feasible, with high patient satisfaction.[40] These alternate genetic counseling delivery approaches need to be studied for provider feasibility and patient acceptability. Several trials at our sites are seeking to explore some of these new delivery models (Table 3).

SPECIAL CHALLENGES IN UNDERSERVED POPULATIONS

Intensive efforts are needed to ensure that genetic assessment is available to underserved populations, which include ethnic and racial minorities, people of low income, and those in rural areas, among others.[41,42] Although rates of germline testing have not been studied in different ethnic and racial subgroups of men with prostate cancer, evidence shows that black and Hispanic women with breast cancer are substantially less likely to undergo genetic testing.[43,44] Reasons for disparities in genetic testing may include differences in physician referrals, distrust and/or lack of understanding of genetics and cancer risk, fear of genetic discrimination on the part of insurers, and disproportionate financial and time burdens for patients with limited resources.[44-50] Ensuring equitable access to genetic testing for black men with prostate cancer may be particularly important, because some preliminary studies show they may be more likely to have germline mutations in *BRCA1* and *BRCA2* than white men.[51] This is compounded by the fact that black men have a 2.4 times greater risk of death from prostate cancer, are more likely to present with late-stage disease, and are significantly less likely to receive definitive treatment than non-Hispanic white men.[52-55]

Improving access to genetic testing in geographically remote areas, where availability of genetic counselors is scare, is also an active area of research. Telephone genetic consults, and other novel genetic assessment, education, and testing delivery methods, show promise.[56] To expand our knowledge and evidence of most effective testing strategies, men with prostate cancer should be offered genetic testing in the setting of clinical trials whenever feasible.

THE CRUCIAL RESPONSIBILITY OF CASCADE TESTING

Cascade testing is the systematic identification of individuals at risk for a hereditary condition through extension of genetic testing to biologic relatives. Although awareness of cascade testing is important in any situation where a germline mutation is identified, it can be particularly important when genetic testing is performed for therapeutic selection. In contrast to patients who pursue genetic testing because of familial cancer risk, those who undergo germline testing for therapy selection may be less aware of the potential implications to family members, because they were not necessarily tested because of an identified familial risk. Moreover, men with prostate cancer are often diagnosed when their children are adults, can pursue testing, and, if positive, undergo enhanced cancer screening or risk-reduction strategies.

There are several known barriers for a patient's communication of results to family members. In *BRCA1/2* screening studies, factors associated with of lack of communication include high worry about genetic risks, low interest or understanding of genomic information, and negative family history.[57-59] Men and second-degree relatives are less likely to pursue genetic testing.[58] Thus, there is an opportunity through education to increase familial communication of results. This panel agrees that when germline testing is performed, the ordering provider should be knowledgeable and work with local cancer genetics experts to offer cascade testing for family members.

CONCLUSION AND FUTURE RESEARCH DIRECTIONS

Recent exciting discoveries in prostate cancer genetics and potential therapeutic interventions with PARP inhibitors and platinum chemotherapies have led to a rapid increase in germline testing for men with mPC. The traditional

framework for genetic testing was developed for individuals believed to be at risk for inherited syndromes, but this model requires adaptation for men with mPC who are increasingly referred for genetic testing to aid in treatment decisions. In this article, we have highlighted special considerations with this treatment-driven ascertainment approach and described areas of research needs (Tables 4 and 5). As the field rapidly evolves, close collaboration between oncologists, urologists, clinical geneticists and counselors, researchers, and indeed, patients themselves, among others, will ensure that we develop the best practices to benefit patients with mPC and their families.

DOI: https://doi.org/10.1200/PO.18.00060
Published online on ascopubs.org/journal/po on August 16, 2018.

AUTHOR CONTRIBUTIONS

Conception and design: Channing J. Paller, Wassim Abida, Joshi J. Alumkal, Daniel J. George, Celestia S. Higano, Akash Patnaik, Charles J. Ryan, Edward M. Schaeffer, Mary-Ellen Taplin, Noah D. Kauff, Jacob Vinson, Emmanuel S. Antonarakis, Heather H. Cheng

Collection and assembly of data: Maria I. Carlo, Veda N. Giri, Channing J. Paller, Tomasz M. Beer, Elisabeth I. Heath, Rana R. McKay, Mary-Ellen Taplin, Noah D. Kauff, Jacob Vinson, Emmanuel S. Antonarakis, Heather H. Cheng

Data analysis and interpretation: Maria I. Carlo, Veda N. Giri, Channing J. Paller, Joshi J. Alumkal, Tomasz M. Beer, Himisha Beltran, Daniel J. George, Elisabeth I. Heath, Rana R. McKay, Alicia K. Morgans, Akash Patnaik, Charles J. Ryan, Walter M. Stadler, Mary-Ellen Taplin, Noah D. Kauff, Jacob Vinson, Emmanuel S. Antonarakis

Manuscript writing: All authors

Final approval of manuscript: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/po/author-center.

Maria I. Carlo
No relationship to disclose

Veda N. Giri
No relationship to disclose

Channing J. Paller
Consulting or Advisory Role: Dendreon
Research Funding: Eli Lilly (Inst)

Wassim Abida
Honoraria: CARET
Consulting or Advisory Role: Clovis Oncology
Research Funding: AstraZeneca, Zenith Epigenetics, Clovis Oncology, GlaxoSmithKline (Inst)
Travel, Accommodations, Expenses: GlaxoSmithKline

Joshi J. Alumkal
Consulting or Advisory Role: Astellas Pharma, Bayer AG, Janssen Biotech
Research Funding: Aragon Pharmaceuticals (Inst), Astellas Pharma (Inst), Novartis (Inst), Zenith Epigenetics (Inst), Gilead Sciences (Inst)

Tomasz M. Beer
Stock and Other Ownership Interests: Salarius Pharmaceuticals
Consulting or Advisory Role: AbbVie, AstraZeneca, Astellas Pharma, Bayer AG, Boehringer Ingelheim, Clovis Oncology, Janssen Biotech, Janssen Oncology, Janssen Research & Development, Johnson & Johnson, Janssen Japan, Merck, Pfizer
Research Funding: Boehringer Ingelheim (Inst), Bristol-Myers Squibb/Medarex (Inst), Janssen Research & Development (Inst), Medivation/Astellas (Inst), Oncogenex (Inst), Sotio (Inst), Sotio, Theraclone Sciences (Inst)

Himisha Beltran
Consulting or Advisory Role: Janssen Oncology, Genzyme, GlaxoSmithKline, AbbVie
Research Funding: Astellas Pharma (Inst), Janssen (Inst), AbbVie/Stemcentrx, Eli Lilly (Inst), Millennium Pharmaceuticals (Inst)

Daniel J. George
Honoraria: Sanofi, Bayer, Exelixis
Consulting or Advisory Role: Bayer AG, Exelixis, Pfizer, Sanofi, Astellas Pharma, Innocrin Pharmaceuticals, Bristol-Myers Squibb, Genentech, Janssen, Merck Sharp & Dohme, Myovant Sciences
Speakers' Bureau: Sanofi, Bayer, Exelixis
Research Funding: Exelixis (Inst), Genentech (Inst), Janssen Oncology (Inst), Novartis (Inst), Pfizer (Inst), Astellas Pharma (Inst), Bristol-Myers Squibb (Inst), Millennium Pharmaceuticals (Inst), Acerta Pharma (Inst), Bayer (Inst), Dendreon (Inst), Innocrin Pharmaceuticals (Inst)
Expert Testimony: Novartis
Travel, Accommodations, Expenses: Bayer AG, Exelixis, Genentech, Medivation, Merck, Pfizer

Elisabeth I. Heath
Honoraria: Bayer, Dendreon, Sanofi

Consulting or Advisory Role: Agensys

Speakers' Bureau: Sanofi

Research Funding: Tokai Pharmaceuticals (Inst), Seattle Genetics (Inst), Agensys (Inst), Dendreon (Inst), Genentech (Inst), Millennium Pharmaceuticals (Inst), Celldex Therapeutics (Inst), Inovio Pharmaceuticals (Inst), Celgene (Inst)

Celestia S. Higano
Employment: CTI BioPharma (I)

Leadership: CTI BioPharma (I)

Stock and Other Ownership Interests: CTI BioPharma (I)

Honoraria: Genentech

Consulting or Advisory Role: Bayer AG, Ferring Pharmaceuticals, Orion, Astellas Pharma, Clovis Oncology, Asana Biosciences, Endocyte, Blue Earth Diagnostics, Myriad Genetics, Tolmar, Janssen

Research Funding: Aragon Pharmaceuticals (Inst), AstraZeneca (Inst), Dendreon (Inst), Genentech (Inst), Medivation (Inst), Emergent BioSolutions (Inst), Bayer (Inst), Pfizer (Inst), Roche (Inst), Astellas Pharma (Inst)

Travel, Accommodations, Expenses: Bayer AG, Astellas Pharma, Clovis Oncology, Blue Earth Diagnostics, Endocyte, Ferring Pharmaceuticals, Genentech, Orion Pharma, Menarini, Myriad Genetics, Pfizer

Rana R. McKay
Consulting or Advisory Role: Janssen, Novartis

Research Funding: Pfizer (Inst), Bayer AG (Inst)

Alicia K. Morgans
Honoraria: Genentech, Janssen, Johnson & Johnson, Sanofi, AstraZeneca

Consulting or Advisory Role: Genentech, AstraZeneca, Sanofi

Akash Patnaik
Honoraria: Clovis Oncology, Merck, Prime Oncology

Consulting or Advisory Role: Janssen Oncology

Research Funding: Bristol-Myers Squibb (Inst), Progenics Pharmaceuticals (Inst), Janssen Oncology (Inst), Clovis Oncology (Inst)

Travel, Accommodations, Expenses: Clovis Oncology, Bristol-Myers Squibb, Merck, Prime Oncology, Janssen Oncology

Charles J. Ryan
Honoraria: Janssen Oncology, Astellas Pharma, Bayer

Consulting or Advisory Role: Bayer AG, Millennium Pharmaceuticals, Ferring Pharmaceuticals

Research Funding: BIND Biosciences, Karyopharm Therapeutics, Novartis

Edward M. Schaeffer
Consulting or Advisory Role: OPKO Diagnostics, AbbVie

Walter M. Stadler
Honoraria: CVS Caremark, Sotio, AstraZeneca, Bristol-Myers Squibb

Consulting or Advisory Role: CVS Caremark, Sotio, AstraZeneca, Bristol-Myers Squibb, Eisai, Bayer AG, Pfizer, Clovis Oncology, Genentech

Research Funding: Bayer AG (Inst), Bristol-Myers Squibb (Inst), Boehringer Ingelheim (Inst), Exelixis (Inst), Novartis (Inst), Genentech (Inst), GlaxoSmithKline (Inst), Medivation (Inst), Pfizer (Inst), Merck (Inst), Millennium Pharmaceuticals (Inst), Janssen (Inst), Johnson & Johnson (Inst), AstraZeneca (Inst), AbbVie (Inst), X4 Pharmaceuticals (Inst), Calithera Biosciences (Inst)

Other Relationship: UpToDate, American Cancer Society

Mary-Ellen Taplin
Honoraria: Janssen-Ortho, Clovis Oncology, Astellas Pharma, Incyte, UpToDate, Research to Practice

Consulting or Advisory Role: Janssen-Ortho, Bayer AG, Guidepoint Global, Best Doctors, UpToDate, Clovis Oncology, Research to Practice, Myovant Sciences, Incyte

Research Funding: Janssen-Ortho (Inst), Medivation (Inst), Bayer (Inst), Tokai Pharmaceuticals (Inst)

Travel, Accommodations, Expenses: Medivation, Janssen Oncology, Tokai Pharmaceuticals, Astellas Pharma, Incyte

Noah D. Kauff
No relationship to disclose

Jacob Vinson
No relationship to disclose

Emmanuel S. Antonarakis
Honoraria: Sanofi, Dendreon, Medivation, Janssen Biotech, ESSA Pharma, Astellas Pharma, Merck, AstraZeneca, Clovis Oncology

Consulting or Advisory Role: Sanofi, Dendreon, Medivation, Janssen Biotech, ESSA Pharma, Astellas Pharma, Merck, AstraZeneca, Clovis Oncology

Research Funding: Janssen Biotech (Inst), Johnson & Johnson (Inst), Sanofi (Inst), Dendreon (Inst), Aragon Pharmaceuticals (Inst), Exelixis (Inst), Millennium Pharmaceuticals (Inst), Genentech (Inst), Novartis (Inst), Astellas Pharma (Inst), Tokai Pharmaceuticals (Inst), Merck (Inst), AstraZeneca (Inst), Clovis Oncology (Inst), Constellation Pharmaceuticals (Inst)

Patents, Royalties, Other Intellectual Property: Co-inventor of a biomarker technology that has been licensed to Qiagen

Travel, Accommodations, Expenses: Sanofi, Dendreon, Medivation

Heather H. Cheng
Research Funding: Inovio Pharmaceuticals, Sanofi, Astellas Medivation, Janssen

ACKNOWLEDGMENT

We thank Mark Robson, MD, for his review and comments on this article.

Affiliations

Maria I. Carlo and **Wassim Abida**, Memorial Sloan-Kettering Cancer Center; **Himisha Beltran**, Weill Cornell Medical Center; **Jacob Vinson**, Prostate Cancer Clinical Trials Consortium, New York, NY; **Veda N. Giri**, Sidney Kimmel Cancer Center at Thomas Jefferson University, Philadelphia, PA; **Channing J. Paller** and **Emmanuel S. Antonarakis**, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; **Joshi J. Alumkal** and **Tomasz M. Beer**, Oregon Health & Science University, Portland, OR; **Daniel J. George** and **Noah D. Kauff**, Duke University, Durham, NC; **Elisabeth I. Heath**, Wayne State University, Detroit, MI; **Celestia S. Higano** and **Heather H. Cheng**, University of Washington and Fred Hutchinson Cancer Research Center, Seattle, WA; **Rana R. McKay**, University of California San Diego, San Diego; **Charles J. Ryan**, University of California San Francisco, San Francisco, CA; **Alicia K. Morgans** and **Edward M. Schaeffer**, Northwestern University Feinberg School of Medicine; **Akash Patnaik** and **Walter M. Stadler**, University of Chicago, Chicago, IL; and **Mary-Ellen Taplin**, Dana-Farber Cancer Institute, Boston, MA.

Support

Supported by the Office of the Assistant Secretary of Defense for Health Affairs, through the Prostate Cancer Research Program under Awards No. W81XWH-17-2-0043, W81XWH-17-2-0018, W81XWH-17-2-0017, W81XWH-17-2-0020, W81XWH-17-2-002, W81XWH-17-2-00221, W81XWH-17-2-0027, and W81XWH-15-2-0018, the Prostate Cancer Foundation (M.I.C., E.S.A., W.A., H.H.C.), the Institute for Prostate Cancer Research, the Pacific Northwest Prostate Cancer National Institutes of Health SPORE Grant No. CA097186, and National Cancer Institute Center Core Grant No. P30 CA008748.

REFERENCES

1. Pritchard CC, Mateo J, Walsh MF, et al: Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med 375:443-453, 2016
2. Mandelker D, Zhang L, Kemel Y, et al: Mutation detection in patients with advanced cancer by universal sequencing of cancer-related genes in tumor and normal DNA vs guideline-based germline testing. JAMA 318:825-835, 2017
3. Pomerantz MM, Spisák S, Jia L, et al: The association between germline BRCA2 variants and sensitivity to platinum-based chemotherapy among men with metastatic prostate cancer. Cancer 123:3532-3539, 2017
4. Mateo J, Carreira S, Sandhu S, et al: DNA-repair defects and olaparib in metastatic prostate cancer. N Engl J Med 373:1697-1708, 2015
5. Cheng HH, Pritchard CC, Boyd T, et al: Biallelic inactivation of BRCA2 in platinum-sensitive metastatic castration-resistant prostate cancer. Eur Urol 69:992-995, 2016
6. Cheng DT, Mitchell TN, Zehir A, et al: Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT): A hybridization capture-based next-generation sequencing clinical assay for solid tumor molecular oncology. J Mol Diagn 17:251-264, 2015
7. Schweizer MT, Antonarakis ES: Prognostic and therapeutic implications of DNA repair gene mutations in advanced prostate cancer. Clin Adv Hematol Oncol 15:785-795, 2017
8. Teply BA, Antonarakis ES: Treatment strategies for DNA repair-deficient prostate cancer. Expert Rev Clin Pharmacol 10:889-898, 2017
9. Antonarakis ES, Lu C, Luber B, et al: Germline DNA-repair gene mutations and outcomes in men with metastatic castration-resistant prostate cancer receiving first-line abiraterone and enzalutamide. Eur Urol 10.1016/j.eururo.2018.01.035 [epub ahead of print on February 10, 2018]
10. Annala M, Struss WJ, Warner EW, et al: Treatment outcomes and tumor loss of heterozygosity in germline DNA repair-deficient prostate cancer. Eur Urol 72:34-42, 2017
11. Mucci LA, Hjelmborg JB, Harris JR, et al: Familial risk and heritability of cancer among twins in Nordic countries. JAMA 315:68-76, 2016
12. National Cancer Institute: Genetics of Prostate Cancer (PDQ)–Health Professional Version. https://www.cancer.gov/types/prostate/hp/prostate–genetics-pdq
13. Isaacsson Velho P, Silberstein JL, Markowski MC, et al: Intraductal/ductal histology and lymphovascular invasion are associated with germline DNA-repair gene mutations in prostate cancer. Prostate 78:401-407, 2018
14. Taylor RA, Fraser M, Livingstone J, et al: Germline BRCA2 mutations drive prostate cancers with distinct evolutionary trajectories. Nat Commun 8:13671, 2017

15. Castro E, Goh C, Olmos D, et al: Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. J Clin Oncol 31:1748-1757, 2013

16. Castro E, Goh C, Leongamornlert D, et al: Effect of BRCA mutations on metastatic relapse and cause-specific survival after radical treatment for localised prostate cancer. Eur Urol 68:186-193, 2015

17. Gallagher DJ, Gaudet MM, Pal P, et al: Germline BRCA mutations denote a clinicopathologic subset of prostate cancer. Clin Cancer Res 16:2115-2121, 2010

18. Na R, Zheng SL, Han M, et al: Germline mutations in ATM and BRCA1/2 distinguish risk for lethal and indolent prostate cancer and are associated with early age at death. Eur Urol 71:740-747, 2017

19. Dowty JG, Win AK, Buchanan DD, et al: Cancer risks for MLH1 and MSH2 mutation carriers. Hum Mutat 34:490-497, 2013

20. Aarnio M, Sankila R, Pukkala E, et al: Cancer risk in mutation carriers of DNA-mismatch-repair genes. Int J Cancer 81:214-218, 1999

21. Haraldsdottir S, Hampel H, Wei L, et al: Prostate cancer incidence in males with Lynch syndrome. Genet Med 16:553-557, 2014

22. Ryan S, Jenkins MA, Win AK: Risk of prostate cancer in Lynch syndrome: A systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 23:437-449, 2014

23. Raymond VM, Mukherjee B, Wang F, et al: Elevated risk of prostate cancer among men with Lynch syndrome. J Clin Oncol 31:1713-1718, 2013

24. Engel C, Loeffler M, Steinke V, et al: Risks of less common cancers in proven mutation carriers with Lynch syndrome. J Clin Oncol 30:4409-4415, 2012

25. Møller P, Seppälä TT, Bernstein I, et al: Cancer risk and survival in path_MMR carriers by gene and gender up to 75 years of age: A report from the Prospective Lynch Syndrome Database. Gut 67:1306-1316, 2018

26. Zehir A, Benayed R, Shah RH, et al: Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. Nat Med 23:703-713, 2017

27. Grindedal EM, Møller P, Eeles R, et al: Germ-line mutations in mismatch repair genes associated with prostate cancer. Cancer Epidemiol Biomarkers Prev 18:2460-2467, 2009

28. Abida W, Armenia J, Gopalan A, et al: Prospective genomic profiling of prostate cancer across disease states reveals germline and somatic alterations that may affect clinical decision making. JCO Precis Oncol, 2017 10.1200/PO.17.00029

29. Le DT, Uram JN, Wang H, et al: PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 372:2509-2520, 2015

30. Gillessen S, Attard G, Beer TM, et al: Management of patients with advanced prostate cancer: The report of the Advanced Prostate Cancer Consensus Conference APCCC 2017. Eur Urol 73:178-211, 2018

31. Giri VN, Knudsen KE, Kelly WK, et al: Role of genetic testing for inherited prostate cancer risk: Philadelphia Prostate Cancer Consensus Conference 2017. J Clin Oncol 36:414-424, 2018

32. Cheng HH, Klemfuss N, Montgomery B, et al: A pilot study of clinical targeted next generation sequencing for prostate cancer: Consequences for treatment and genetic counseling. Prostate 76:1303-1311, 2016

33. Abida W, Armenia J, Gopalan A, et al: Prospective genomic profiling of prostate cancer across disease states reveals germline and somatic alterations that may affect clinical decision making. JCO Precis Oncol, 2017 10.1200/PO.17.00029

34. Hampel H, Pearlman R, Beightol M, et al: Assessment of tumor sequencing as a replacement for Lynch syndrome screening and current molecular tests for patients with colorectal cancer. JAMA Oncol 4:806-813, 2018

35. Middha S, Zhang L, Nafa K, et al: Reliable pan-cancer microsatellite instability assessment by using targeted next-generation sequencing data. JCO Precis Oncol, 2017 10.1200/PO.17.00084

36. Hamilton JG, Shuk E, Genoff MC, et al: Interest and attitudes of patients with advanced cancer with regard to secondary germline findings from tumor genomic profiling. J Oncol Pract 13:e590-e601, 2017

37. Hamilton JG, Shuk E, Garzon MG, et al: Decision-making preferences about secondary germline findings that arise from tumor genomic profiling among patients with advanced cancers. JCO Precis Oncol, 2017 10.1200/PO.17.00182

38. Fox E, McCuaig J, Demsky R, et al: The sooner the better: Genetic testing following ovarian cancer diagnosis. Gynecol Oncol 137:423-429, 2015 [Erratum: Gynecol Oncol 145:409, 2017]

39. Percival N, George A, Gyertson J, et al: The integration of BRCA testing into oncology clinics. Br J Nurs 25:690-694, 2016

40. Colombo N, Huang G, Scambia G, et al: Evaluation of a streamlined oncologist-led BRCA mutation testing and counseling model for patients with ovarian cancer. J Clin Oncol36:1300-1307, 2017

41. Hawkins AK, Hayden MR: A grand challenge: Providing benefits of clinical genetics to those in need. Genet Med 13:197-200, 2011

42. Hall MJ, Olopade OI: Disparities in genetic testing: Thinking outside the BRCA box. J Clin Oncol 24:2197-2203, 2006

43. Jones T, McCarthy AM, Kim Y, et al: Predictors of BRCA1/2 genetic testing among Black women with breast cancer: A population-based study. Cancer Med 6:1787-1798, 2017

44. Levy DE, Byfield SD, Comstock CB, et al: Underutilization of BRCA1/2 testing to guide breast cancer treatment: Black and Hispanic women particularly at risk. Genet Med 13:349-355, 2011

45. Allford A, Qureshi N, Barwell J, et al: What hinders minority ethnic access to cancer genetics services and what may help? Eur J Hum Genet 22:866-874, 2014

46. Armstrong K, Calzone K, Stopfer J, et al: Factors associated with decisions about clinical BRCA1/2 testing. Cancer Epidemiol Biomarkers Prev 9:1251-1254, 2000

47. Hughes C, Gomez-Caminero A, Benkendorf J, et al: Ethnic differences in knowledge and attitudes about BRCA1 testing in women at increased risk. Patient Educ Couns 32:51-62, 1997

48. Shields AE, Burke W, Levy DE: Differential use of available genetic tests among primary care physicians in the United States: Results of a national survey. Genet Med 10:404-414, 2008

49. Thompson HS, Sussner K, Schwartz MD, et al: Receipt of genetic counseling recommendations among black women at high risk for BRCA mutations. Genet Test Mol Biomarkers 16:1257-1262, 2012

50. Vadaparampil ST, Wideroff L, Breen N, et al: The impact of acculturation on awareness of genetic testing for increased cancer risk among Hispanics in the year 2000 National Health Interview Survey. Cancer Epidemiol Biomarkers Prev 15:618-623, 2006

51. Petrovics G, Ravindranath L, Chen Y, et al: Higher frequency of germline BRCA1 and BRCA2 mutations in African American prostate cancer. J Urol 195:e548, 2016

52. Moses KA, Orom H, Brasel A, et al: Racial/ethnic disparity in treatment for prostate cancer: Does cancer severity matter? Urology 99:76-83, 2017

53. Merrill RM, Lyon JL: Explaining the difference in prostate cancer mortality rates between white and black men in the United States. Urology 55:730-735, 2000

54. Paller CJ, Cole AP, Partin AW, et al: Risk factors for metastatic prostate cancer: A sentinel event case series. Prostate 77:1366-1372, 2017

55. Taksler GB, Keating NL, Cutler DM: Explaining racial differences in prostate cancer mortality. Cancer 118:4280-4289, 2012

56. Kinney AY, Butler KM, Schwartz MD, et al: Expanding access to BRCA1/2 genetic counseling with telephone delivery: A cluster randomized trial. J Natl Cancer Inst 106:dju328, 2014

57. Elrick A, Ashida S, Ivanovich J, et al: Psychosocial and clinical factors associated with family communication of cancer genetic test results among women diagnosed with breast cancer at a young age. J Genet Couns 26:173-181, 2017

58. Lieberman S, Lahad A, Tomer A, et al: Familial communication and cascade testing among relatives of BRCA population screening participants. Genet Med 10.1038/gim.2018.26 [Epub ahead of print March 29, 2018]

59. Cheung EL, Olson AD, Yu TM, et al: Communication of BRCA results and family testing in 1,103 high-risk women. Cancer Epidemiol Biomarkers Prev 19:2211-2219, 2010

Appendix

Table A1. Selected Genes Associated With Treatment Implications and Predisposition to Prostate Cancer

Gene	Potential Treatment/Clinical Trials With Inclusion of Alteration (germline and/or somatic)	Level of Evidence Suggesting Predisposition to Prostate Cancer*	Predisposition Risk Conferred	Association With Aggressive Disease
BRCA2	Yes	A	RR, 3-8	Yes
BRCA1	Yes	A	RR, 2-4	Yes
ATM	Yes	C	Not established	Emerging
CHEK2	Yes	D		
PALB2	Yes	D		
RAD51D	Yes	D		
ATR	Yes	D		
NBN	Yes	C	Not established	
MLH1	Yes	B	Conflicting (RR, 1-6)	
MSH2	Yes	B	Conflicting (RR, 1-6)	
MSH6	Yes	B	Conflicting (RR, 1-6)	
PMS2	Yes	B	Conflicting (RR, 1-6)	
HOXB13 (p.G84E)	No	A	OR, 2-8	

Abbreviations: OR, odds ratio; RR, relative risk.

*Adapted from Giri et al.[31] Levels of evidence: (A) high-grade evidence: at least one prospectively designed study or three or more large validation studies or three or more descriptive studies; (B) moderate-grade evidence: two cohort or case-control studies; (C) emerging data: increasing data in support of association to prostate cancer, but not yet moderate-grade evidence; (D) low/insufficient: limited data or not studied in the context of prostate cancer.

Metastatic Hormone-Sensitive Prostate Cancer: Clinical Decision Making in a Rapidly Evolving Landscape of Life-Prolonging Therapy

David J. VanderWeele, MD, PhD[1]; Emmanuel S. Antonarakis, MD[2]; Michael A. Carducci, MD[2]; Robert Dreicer, MD, MS[3]; Karim Fizazi, MD, PhD[4]; Silke Gillessen, MD[5]; Celeste S. Higano, MD[6]; Alicia K. Morgans, MD, MPH[1]; Daniel P. Petrylak, MD[7]; Christopher J. Sweeney, MBBS[8]; and Maha Hussain, MD[1]

Background

The majority of men who die as a result of metastatic prostate cancer developed castration-resistant disease that progressed from an earlier hormone-sensitive state. In 2004, the first life-prolonging therapy, docetaxel (DOC), was approved by the US Food and Drug Administration for metastatic castration-resistant prostate cancer (mCRPC). Since 2010, five additional agents were approved for mCRPC on the basis of prolonging median overall survival (OS) by up to 5 months: sipuleucel-T, cabazitaxel, abiraterone plus prednisone (AAP), enzalutamide (ENZA), and radium-223.[1-7] Recent practice-changing trials have demonstrated that rationally intensifying treatment of metastatic hormone-sensitive prostate cancer (mHSPC), by advancing effective therapy for mCRPC to the hormone-sensitive state, has a bigger impact on OS. This treatment includes DOC (CHAARTED [Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer] trial supported by STAMPEDE [Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy] Arm C and GETUG-15), AAP (LATITUDE [Abiraterone Acetate Plus Prednisone in Patients With Newly Diagnosed High-Risk Metastatic Castration-Sensitive Prostate Cancer] with additional support from STAMPEDE Arm G), ENZA (ENZAMET [Enzalutamide in First-Line Androgen-Deprivation Therapy for Metastatic Prostate Cancer], with support from ARCHES [Enzalutamide Plus Androgen-Deprivation Therapy for Metastatic Hormone-Sensitive Prostate Cancer]), and apalutamide (APA; TITAN [Apalutamide Plus Androgen-Deprivation Therapy (ADT) Versus ADT in Patients With Metastatic Hormone-Sensitive Prostate Cancer] trial).[8-14] The hazard ratios (HRs) for these agents in mHSPC are similar to those in mCRPC. Because OS is longer for mHSPC, however, these therapies have a larger absolute effect in this setting, with an unprecedented increase in median OS by more than 1 year. This supports the basic principle in oncology that advancement of effective therapies to earlier stages of disease leads to better therapeutic impact, with four agents now demonstrating improved survival in this setting.

Although encouraging, these trials leave us with several unanswered questions: How do we best personalize therapy on the basis of clinical subgroups? What is the role of focal therapy in the setting of effective systemic therapy? How should we incorporate molecular characteristics into management?

Clinical Subgroups

Selection of which agent to use for mHSPC is guided in part by disease burden, which is based on conventional imaging (computed tomography and bone scan). For more than 30 years, it has been recognized that prognosis in mHSPC is informed by the extent of disease burden.[15] The definitions of low volume/risk versus high volume/risk have varied, driven by metastases location[15-17] and/or number[18] of bone metastases. The CHAARTED trial was positive overall and supported androgen-deprivation therapy (ADT) plus DOC for patients with mHSPC.[9] A priori stratification was based in part on disease volume, with high volume defined as either visceral metastases or four or more bone lesions with one or more lesions beyond the axial skeleton per conventional imaging. The improvement in OS from DOC was primarily driven by benefit in patients with high-volume disease (HR, 0.63); there was no significant impact on OS in patients with low-volume disease[19] (HR, 1.04; Table 1). A similar result was seen in the post hoc analysis of GETUG-15.[20] CHAARTED was not powered for this subgroup analysis, however, and the subgroup was small. Post hoc analysis of STAMPEDE Arm C, expected to be reported later this year, will provide additional evidence.

In contrast, the benefit of the androgen receptor pathway inhibitors (ARPIs) AAP, ENZA, and APA seem to apply to all patients with mHSPC, regardless of disease burden. LATITUDE evaluated AAP in patients with high-risk disease (defined by Gleason score

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on July 30, 2019 and published at jco.org on September 10, 2019: DOI https://doi.org/10.1200/JCO.19.01595

TABLE 1. Phase III Trials for Metastatic Hormone-Sensitive Prostate Cancer

Trial	Clinical Trials Information	Comparator Arm	Control Arm	No. of Trial Participants	PFS, HR or EP	OS, HR or EP	First Author or Status
Reported trials							
High volume/high risk							
Docetaxel							
CHAARTED	NCT00309985	ADT + DOC	ADT	513	0.58 (time to CRPC)	0.63	Kyriakopoulos[19]
GETUG-15	NCT00104715	ADT + DOC	ADT	183	NA	0.78	Gravis[20]
STAMPEDE Arm C	NCT00268476	ADT + DOC	ADT	724	NA	TBD	James[10]
ARPI							
LATITUDE	NCT01715285	ADT + AAP	ADT	955	NA	0.62	Fizazi[21]
STAMPEDE Arm G	NCT00268476	ADT + AAP	ADT	473	0.31 (FFS)	0.54	Hoyle[22]
ENZAMET	NCT02446405	ADT + ENZA (± DOC)	ADT + NSAA (± DOC)	588	0.45	0.80	Davis[13]
ARCHES	NCT02677896	ADT + ENZA (prior DOC allowed)	ADT (prior DOC allowed)	727	0.44 (rPFS)	TBD	Armstrong[23]
TITAN	NCT02489318	ADT + APA (prior DOC allowed)	ADT (prior DOC allowed)	660	0.53	0.68	Chi[14]
RT							
STAMPEDE Arm H	NCT00268476	RT to prostate	ADT (+ DOC possible)	1,120	NA	1.07	Parker[25]
HORRAD	ISRCTN06890529	RT to prostate	ADT	272	NA	1.06	Boevé[26]
Low volume/low risk							
Docetaxel							
CHAARTED	NCT00309985	ADT + DOC	ADT	277	0.70 (Time to CRPC)	1.04	Kyriakopoulos[19]
GETUG-15	NCT00104715	ADT + DOC	ADT	202	NA	0.9	Gravis[20]
STAMPEDE Arm C	NCT00268476	ADT + DOC	ADT	362	NA	TBD	James[10]
ARPI							
LATITUDE	NCT01715285	ADT + AAP	ADT	243	NA	0.72	Fizazi[21]
STAMPEDE Arm G	NCT00268476	ADT + AAP	ADT	428	0.24 (FFS)	0.66	Hoyle[22]
ENZAMET	NCT02446405	ADT + ENZA (± DOC)	ADT + NSAA (± DOC)	537	0.30	0.43	Davis[13]
ARCHES	NCT02677896	ADT + ENZA (prior DOC allowed)	ADT (prior DOC allowed)	423	0.24 (rPFS)	TBD	Armstrong[23]
TITAN	NCT02489318	ADT + APA (prior DOC allowed)	ADT (prior DOC allowed)	392	0.36	0.67	Chi[14]

(continued on following page)

TABLE 1. Phase III Trials for Metastatic Hormone-Sensitive Prostate Cancer (continued)

Trial	Clinical Trials Information	Comparator Arm	Control Arm	No. of Trial Participants	PFS, HR or EP	OS, HR or EP	First Author or Status
RT							
STAMPEDE Arm H	NCT00268476	RT to prostate	ADT (+ DOC possible)	819	NA	0.68 (OS)	Parker[25]
HORRAD	ISRCTN06890529	RT to prostate	ADT	160	NA	0.68 (OS)	Boevé[26]
Not-reported trials							
ARPI							
STAMPEDE Arm J	NCT00268476	ADT + AAP + ENZA (DOC)	ADT (DOC)	1,800		Primary EP	Completed accrual 2016
PEACE-1	NCT01957436	ADT + DOC + AAP (± RT)	ADT + DOC (± RT)	1,173	Coprimary EP	Coprimary EP	Completed accrual 2018
ARASENS	NCT02799602	ADT + DOC + darolutamide	ADT + DOC	1,303		Primary EP	Complete approximately 2022
SWOG-1216	NCT01809691	ADT + orterenel	ADT + bicalutamide	1,313		Primary EP	Complete approximately 2022
RT							
PEACE-1	NCT01957436	ADT + DOC ± AAP + RT	ADT + DOC ± AAP	1,173	Coprimary EP	Coprimary EP	Completed accrual 2018
PLATON	NCT03784755	SST + ablative therapy for all sites	SST + ablative therapy for prostate	410	Primary EP		Complete approximately 2025
SWOG-1802	NCT03678025	SST + definitive treatment of prostate	SST	1,273		Primary EP	Complete approximately 2028

Abbreviations: AAP, abiraterone acetate plus prednisone; ADT, androgen-deprivation therapy; APA, apalutamide; ARASENS, ODM-201 in Addition to Standard Androgen-Deprivation Therapy and Docetaxel in Metastatic Castration-Sensitive Prostate Cancer; ARCHES, Enzalutamide Plus ADT for Metastatic Hormone-Sensitive Prostate Cancer; CHAARTED, Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer; ARPI, androgen receptor pathway inhibitor; CRPC, castration-resistant prostate cancer; DOC, docetaxel; ENZA, enzalutamide; ENZAMET, Enzalutamide in First-Line Androgen-Deprivation Therapy for Metastatic Prostate Cancer; EP, end point; FFS, failure-free survival; HORRAD, Hormonal Therapy Versus Hormonal Therapy Plus Local External Radiation Therapy in Patients With Primary Diagnosed Metastasized Prostate Cancer; HR, hazard ratio; LATITUDE, Abiraterone Acetate Plus Prednisone in Patients With Newly Diagnosed High-Risk Metastatic Castration-Sensitive Prostate Cancer; NA, not available; NSAA, nonsteroidal anti-androgen; OS, overall survival; PFS, progression-free survival; PLATON, Local Ablative Therapy for Hormone-Sensitive Oligometastatic Prostate Cancer; rPFS, radiographic progression-free survival; RT, radiotherapy; SST, standard systemic therapy; STAMPEDE, Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy; TBD, to be determined; TITAN, Apalutamide Plus Androgen-Deprivation Therapy (ADT) Versus ADT in Patients With Metastatic Hormone-Sensitive Prostate Cancer.

together with sites and number of metastases on conventional imaging) and showed survival improvement for these men.[11,21] Post hoc subgroup analysis of LATITUDE by disease volume (CHAARTED definition) confirmed benefit across subgroups, although the *P* value for benefit in low-volume disease was not significant. STAMPEDE Arm G included patients with metastatic high- or low-risk/volume disease (52%) and patients with high-risk nonmetastatic disease (48%) and was positive for OS in the whole population (HR, 0.63).[12] Post hoc analysis of patients with metastatic disease demonstrated improved OS in both high- and low-risk groups (LATITUDE definition; high-risk HR, 0.54; low-risk HR, 0.66). Similar results were seen in high- and low-volume disease (per CHAARTED definition).[22] ENZAMET (HR, 0.67) and TITAN (HR, 0.68) were both positive in the overall patient population, with benefit seen in high- and low-volume disease for ENZA and APA, respectively (ENZA HRs, 0.80 and 0.43; APA HRs, 0.68 and 0.67). Thus, the totality of the data indicates that patients with lower disease burden also benefit from earlier AAP. Of note, in ENZAMET and TITAN, there seemed to be less benefit of an ARPI for patients who also received DOC, which likely had a greater effect on the HR for those with high-volume disease than with low-volume disease. These studies generally excluded patients with histologies other than adenocarcinoma; poor performance status; recent cardiac events; or, for the trials involving anti-androgens, prior seizure, and the balancing of risks and benefits is critical in considering therapy intensification in these patients.

Although subgroup evaluation of volume/risk is informative, more is needed to personalize therapy better. Patients with metastases only in the lung, for example, are considered high volume/risk as a result of having visceral metastases, yet they may actually have prolonged responses to ADT alone.[24] The evolution of imaging technologies is a major confounding factor in the context of both those with M1 disease by conventional imaging and those with M0 disease by conventional imaging but M1 disease on next-generation imaging (eg, fluciclovine positron emission tomography or prostate-specific membrane antigen–targeted imaging). Trials to date have not incorporated next-generation imaging, and as such, how to factor in newer imaging for management decisions is not clear. Future trials should seek to refine subgroup definitions by incorporating newer imaging techniques and prospectively evaluating subgroup-specific therapy.

Focal Therapy

The role of local therapy to the prostate has been a subject of interest for decades but with no definitive data. The radiotherapy (RT) arm of STAMPEDE (Arm H) evaluated the impact of prostate RT in patients with mHSPC. After Arm H was fully accrued, the investigators annotated patients' volume of disease, having hypothesized that RT would be more beneficial in patients with low-volume mHSPC, and before analysis, specified these subgroups and powered Arm H accordingly. Improvement in failure-free survival with the addition of prostate RT was found for all patients (HR, 0.76). There was no OS benefit in the overall population (HR, 0.92), but patients with low-volume disease had an improved OS (HR, 0.68).[25] A similar effect was observed in the HORRAD (Hormonal Therapy Versus Hormonal Therapy Plus Local External Radiation Therapy in Patients With Primary Diagnosed Metastasized Prostate Cancer) trial for those with fewer than five metastases (HR, 0.68) and is summarized in a meta-analysis.[26,27] In both trials, ADT alone was the treatment for the majority of patients; in STAMPEDE, 16% of patients received additional DOC.

The role of radiation to oligometastatic disease has been an area of significant interest as well. Many patients with low-volume disease have oligometastatic disease by conventional imaging, and the question is whether they will benefit from RT to all sites of disease.[28] To date, trials that have evaluated metastasis-directed therapy have focused on delaying the initiation of ADT rather than on improvement in OS. This was true in STOMP (Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence), which targeted up to three metastases seen on next-generation imaging (choline positron emission tomography-computed tomography), and in ORIOLE (Observation Versus Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer), an ongoing trial that targets up to three metastases seen on conventional imaging.[28,29] No definitive data support the survival benefit of this strategy, although several ongoing trials are evaluating the role of focal therapy in various settings. PEACE-1 is evaluating the role of local RT and/or AAP addition to ADT and DOC regardless of disease volume/risk, both for OS and for effect on local symptoms. The PLATON (Local Ablative Therapy for Hormone-Sensitive Oligometastatic Prostate Cancer) trial is comparing ablative therapy to the prostate versus to all sites of oligometastatic disease. Of note, patients in this trial are allowed to discontinue systemic therapy, which for the first time allows evaluation for cure with a combination systemic therapy and focal therapy approach. SWOG-1802 is testing the role of definitive therapy to the prostate, regardless of disease volume. The innovative design of SWOG-1802 offers definitive therapy only to those who are still responding to systemic therapy after 22 to 28 weeks, which thus spares those with primary refractory disease. It addresses whether the benefit of local prostate cancer control can be extended to more patients and whether treating the primary is relevant in an era of more-effective systemic therapy (akin to CARMENA [Clinical Trial to Assess the Importance of Nephrectomy], which replaces interferon with more-effective tyrosine kinase inhibitors).[30] In addition to improvements in survival, SWOG-1802 and PEACE-1 are evaluating treatment effects on quality of life.

Molecular Characteristics

One way to improve upon risk stratification using disease-volume/risk subgroups is to incorporate molecular characteristics. In mCRPC, defects in the tumor suppressor genes *PTEN*, *RB1*, and *TP53* are associated with aggressive-variant prostate cancer, and patients with these alterations may benefit from platinum-based therapy.[31,32] Data suggest that loss of these genes also may inform risk in mHSPC because patients with intact tumor suppressor genes do well on ADT alone.[33] Similarly, decisions about the addition of local therapy to the prostate would be better personalized if they incorporated molecular characteristics of the disease. For example, the gene expression assay Decipher (Decipher Biosciences, San Diego, CA) predicts benefit from adjuvant or salvage RT.[34] Its performance in the metastatic setting is unknown.

To date, treatment of mHSPC is not biomarker targeted. The exception is the tissue agnostic indication in the United States for pembrolizumab for microsatellite instability-high or mismatch repair–deficient solid tumors. Numerous reports have cataloged the genomic landscape of localized prostate cancer or mCRPC.[35-40] Those that examined mHSPC have suggested that the same genetic alterations are present in this disease state, with frequencies intermediate between localized disease and CRPC.[33,41,42] These include loss of function of *PTEN* and DNA repair genes. (The major exception is androgen receptor alterations that arise only in mCRPC.) Early-phase trials have demonstrated in mCRPC the ability to target deficiency in DNA repair with poly (ADP-ribose) polymerase inhibitors or carboplatin and *PTEN* loss with phosphatidylinositol 3-kinase or AKT inhibitors.[32,41-47] When moved to mHSPC (in patients with the appropriate genomic profile), these therapies may improve outcomes more dramatically.

Current Practice in Response to Available Data

Many physicians understandably are concerned about making major changes to their practice on the basis of subgroup analyses of the trials described herein, some of which are post hoc. It comes down to a desire for conclusive data versus a willingness to tolerate some imperfection and to make the best decision possible on the basis of the data available. The trials that generate these results took many years to conduct and the willing participation of thousands of patients internationally. The generation of conclusive data about the proper setting to use DOC, an ARPI, and/or RT to the prostate would require many more years and many more patients, a large cost for validating a result that already has high confidence.

We take a pragmatic approach to interpreting these newly available results and conclude that they are sufficient to change practice but do not preclude further studies to confirm their value moving forward. As part of our pragmatic approach, we propose that pending conclusive data in patients with low-volume oligometastatic mHSPC on conventional imaging, it is reasonable to consider intensified therapy with ADT + ARPI, radiation to the prostate, and potentially radiation to metastatic sites, with an acknowledgment that fewer data exist for the latter approach. Moreover, if the patient achieves an undetectable prostate-specific antigen with durable control (eg, more than 2 to 3 years), it is reasonable to halt systemic therapy, especially if adverse events that are metabolic and quality-of-life impairing emerge, and observe until biochemical progression. Not all these strategies are supported by level 1 evidence at this time and should be undertaken on the basis of informed shared decisions that balance risks/benefits, comorbidities, emerging data, and patient preferences. In the meantime, the trials that test these hypotheses should continue, and patients preferentially should be offered the opportunity to participate in these trials. Individual patient data registries or meta-analyses, which depend on a global willingness for data sharing, will provide greater granularity on outcomes by subgroup in the real world. These are planned or ongoing.

In conclusion, since 2015, there has been significant improvement in survival for patients with mHSPC, with an unprecedented "return on investment" from DOC and ARPIs. Refinement of clinical subgroups and incorporation of molecular characteristics will help to personalize therapy by identifying for whom and how to intensify therapy. Yet, we remain far from eradicating metastatic disease. Continued discovery and evaluation of novel therapeutic vulnerabilities and a better understanding of mechanisms of resistance are critical to transforming care. These efforts to expand the patient populations that experience an exceptional response to systemic therapy will convert metastatic prostate cancer from deadly to chronic on our way to potential cure.

AFFILIATIONS

[1]Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL
[2]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD
[3]University of Virginia Cancer Center, Charlottesville, VA
[4]Institut Gustave Roussy, University of Paris Sud, Villejuif, France
[5]Manchester Cancer Research Centre, Manchester, United Kingdom
[6]Fred Hutchinson Cancer Research Center, Seattle, WA
[7]Yale University School of Medicine, New Haven, CT
[8]Dana-Farber Cancer Institute, Boston, MA

CORRESPONDING AUTHOR

Maha Hussain, MD, Division of Hematology/Oncology, Robert H. Lurie Comprehensive Cancer Center of Northwestern University, 303 E Superior St, Chicago, IL 60611; e-mail: maha.hussain@northwestern.edu.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.19.01595.

AUTHOR CONTRIBUTIONS

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

REFERENCES

1. Kantoff PW, Higano CS, Shore ND, et al: Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 363:411-422, 2010
2. de Bono JS, Oudard S, Ozguroglu M, et al: Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: A randomised open-label trial. Lancet 376:1147-1154, 2010
3. de Bono JS, Logothetis CJ, Molina A, et al: Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 364:1995-2005, 2011
4. Scher HI, Fizazi K, Saad F, et al: Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 367:1187-1197, 2012
5. Parker C, Nilsson S, Heinrich D, et al: Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med 369:213-223, 2013
6. Ryan CJ, Smith MR, de Bono JS, et al: Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 368:138-148, 2013
7. Beer TM, Armstrong AJ, Rathkopf DE, et al: Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 371:424-433, 2014
8. Gravis G, Fizazi K, Joly F, et al: Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): A randomised, open-label, phase 3 trial. Lancet Oncol 14:149-158, 2013
9. Sweeney CJ, Chen Y-H, Carducci M, et al: Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med 373:737-746, 2015
10. James ND, Sydes MR, Clarke NW, et al: Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): Survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet 387:1163-1177, 2016
11. Fizazi K, Tran N, Fein L, et al: Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med 377:352-360, 2017
12. James ND, de Bono JS, Spears MR, et al: Abiraterone for prostate cancer not previously treated with hormone therapy. N Engl J Med 377:338-351, 2017
13. Davis ID, Martin AJ, Stockler MR, et al: Enzalutamide with standard first-line therapy in metastatic prostate cancer. N Engl J Med 381:121-131, 2019
14. Chi KN, Agarwal N, Bjartell A, et al: Apalutamide for metastatic, castration-sensitive prostate cancer. N Engl J Med 381:13-24, 2019
15. Crawford ED, Eisenberger MA, McLeod DG, et al: A controlled trial of leuprolide with and without flutamide in prostatic carcinoma. N Engl J Med 321:419-424, 1989
16. Hussain M, Tangen CM, Berry DL, et al: Intermittent versus continuous androgen deprivation in prostate cancer. N Engl J Med 368:1314-1325, 2013
17. Eisenberger MA, Blumenstein BA, Crawford ED, et al: Bilateral orchiectomy with or without flutamide for metastatic prostate cancer. N Engl J Med 339: 1036-1042, 1998
18. Millikan RE, Wen S, Pagliaro LC, et al: Phase III trial of androgen ablation with or without three cycles of systemic chemotherapy for advanced prostate cancer. J Clin Oncol 26:5936-5942, 2008
19. Kyriakopoulos CE, Chen Y-H, Carducci MA, et al: Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: Long-term survival analysis of the randomized phase III E3805 CHAARTED trial. J Clin Oncol 36:1080-1087, 2018
20. Gravis G, Boher J-M, Joly F, et al: Androgen deprivation therapy (ADT) plus docetaxel versus ADT alone in metastatic non castrate prostate cancer: Impact of metastatic burden and long-term survival analysis of the randomized phase 3 GETUG-AFU15 trial. Eur Urol 70:256-262, 2016
21. Fizazi K, Tran N, Fein L, et al: Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): Final overall survival analysis of a randomised, double-blind, phase 3 trial. Lancet Oncol 20:686-700, 2019
22. Hoyle AP, Ali A, James ND, et al: The role of abiraterone acetate plus prednisone/prednisolone in high- and low-risk metastatic hormone sensitive prostate cancer. Eur Urol Suppl 18:e1387-e1388, 2019
23. Armstrong AJ, Szmulewitz RZ, Petrylak DP, et al: ARCHES: A randomized, phase III study of androgen-deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer. J Clin Oncol 10.1200/JCO.19.00799 [epub ahead of print on July 22, 2019]
24. Shenderov E, Velho PI, Awan AH, et al: Genomic characterization of pulmonary-metastatic prostate cancer: A unique molecular subtype. J Clin Oncol 37, 2019 (suppl; abstr 210)
25. Parker CC, James ND, Brawley CD, et al: Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): A randomised controlled phase 3 trial. Lancet 392:2353-2366, 2018
26. Boevé LMS, Hulshof MCCM, Vis AN, et al: Effect on survival of androgen deprivation therapy alone compared to androgen deprivation therapy combined with concurrent radiation therapy to the prostate in patients with primary bone metastatic prostate cancer in a prospective randomised clinical trial: Data from the HORRAD trial. Eur Urol 75:410-418, 2019
27. Burdett S, Boevé LM, Ingleby FC, et al: Prostate radiotherapy for metastatic hormone-sensitive prostate cancer: A STOPCAP systematic review and meta-Analysis. Eur Urol 76:115-124, 2019
28. Radwan N, Phillips R, Ross A, et al: A phase II randomized trial of observation versus stereotactic ablative RadiatIon for oligometastatic prostate cancer (ORIOLE). BMC Cancer 17:453, 2017
29. Ost P, Reynders D, Decaestecker K, et al: Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: A prospective, randomized, multicenter phase II trial. J Clin Oncol 36:446-453, 2018
30. Méjean A, Ravaud A, Thezenas S, et al: Sunitinib alone or after nephrectomy in metastatic renal-cell carcinoma. N Engl J Med 379:417-427, 2018
31. Aparicio AM, Shen L, Tapia ELN, et al: Combined tumor suppressor defects characterize clinically defined aggressive variant prostate cancers. Clin Cancer Res 22:1520-1530, 2016
32. Aparicio AM, Harzstark AL, Corn PG, et al: Platinum-based chemotherapy for variant castrate-resistant prostate cancer. Clin Cancer Res 19:3621-3630, 2013
33. Hamid AA, Gray KP, Shaw G, et al: Compound genomic alterations of TP53, PTEN, and RB1 tumor suppressors in localized and metastatic prostate cancer. Eur Urol 76:89-97, 2019
34. Dalela D, Santiago-Jiménez M, Yousefi K, et al: Genomic classifier augments the role of pathological features in identifying optimal candidates for adjuvant radiation therapy in patients with prostate cancer: Development and internal validation of a multivariable prognostic model. J Clin Oncol 35:1982-1990, 2017
35. Cancer Genome Atlas Research Network: The molecular taxonomy of primary prostate cancer. Cell 163:1011-1025, 2015
36. Taylor BS, Schultz N, Hieronymus H, et al: Integrative genomic profiling of human prostate cancer. Cancer Cell 18:11-22, 2010

37. Fraser M, Sabelnykova VY, Yamaguchi TN, et al: Genomic hallmarks of localized, non-indolent prostate cancer. Nature 541:359-364, 2017
38. Grasso CS, Wu Y-M, Robinson DR, et al: The mutational landscape of lethal castration-resistant prostate cancer. Nature 487:239-243, 2012
39. Kumar A, White TA, MacKenzie AP, et al: Exome sequencing identifies a spectrum of mutation frequencies in advanced and lethal prostate cancers. Proc Natl Acad Sci U S A 108:17087-17092, 2011
40. Robinson D, Van Allen EM, Wu Y-M, et al: Integrative clinical genomics of advanced prostate cancer. Cell 161:1215-1228, 2015 [Erratum: Cell 162:454, 2015]
41. Hovelson DH, McDaniel AS, Cani AK, et al: Development and validation of a scalable next-generation sequencing system for assessing relevant somatic variants in solid tumors. Neoplasia 17:385-399, 2015
42. Abida W, Armenia J, Gopalan A, et al: Prospective genomic profiling of prostate cancer across disease states reveals germline and somatic alterations that may affect clinical decision making. JCO Precis Oncol 10.1200/PO.17.00029
43. Mateo J, Carreira S, Sandhu S, et al: DNA-repair defects and olaparib in metastatic prostate cancer. N Engl J Med 373:1697-1708, 2015
44. Clarke N, Wiechno P, Alekseev B, et al: Olaparib combined with abiraterone in patients with metastatic castration-resistant prostate cancer: A randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Oncol 19:975-986, 2018
45. Hamid AA, Gray KP, Shaw G, et al: Compound genomic alterations of TP53, PTEN, and RB1 tumor suppressors in localized and metastatic prostate cancer. Eur Urol 76:89-97, 2019
46. Cheng HH, Pritchard CC, Boyd T, et al: Biallelic inactivation of BRCA2 in platinum-sensitive metastatic castration-resistant prostate cancer. Eur Urol 69: 992-995, 2016
47. de Bono JS, De Giorgi U, Rodrigues DN, et al: Randomized phase II study evaluating Akt blockade with ipatasertib, in combination with abiraterone, in patients with metastatic prostate cancer with and without PTEN loss. Clin Cancer Res, 25:928-936, 2018

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Metastatic Hormone-Sensitive Prostate Cancer: Clinical Decision Making in a Rapidly Evolving Landscape of Life-Prolonging Therapy

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

David J. VanderWeele
Travel, Accommodations, Expenses: Genzyme

Emmanuel S. Antonarakis
Honoraria: Sanofi, Dendreon, Medivation, Janssen Pharmaceuticals, ESSA, Astellas Pharma, Merck, AstraZeneca, Clovis Oncology
Consulting or Advisory Role: Sanofi, Dendreon, Medivation, Janssen Pharmaceuticals, ESSA, Astellas Pharma, Merck, AstraZeneca, Clovis Oncology
Research Funding: Janssen Pharmaceuticals (Inst), Johnson & Johnson (Inst), Sanofi, (Inst), Dendreon (Inst), Aragon Pharmaceuticals (Inst), Exelixis (Inst), Millennium Pharmaceuticals (Inst), Genentech (Inst), Novartis (Inst), Astellas Pharma (Inst), Tokai Pharmaceuticals (Inst), Merck (Inst), AstraZeneca (Inst), Clovis Oncology (Inst), Constellation Pharmaceuticals (Inst)
Patents, Royalties, Other Intellectual Property: Co-inventor of a biomarker technology that has been licensed to QIAGEN
Travel, Accommodations, Expenses: Sanofi, Dendreon, Medivation

Michael A. Carducci
Consulting or Advisory Role: Astellas Pharma, AbbVie, Roche, Genentech, Pfizer, Foundation Medicine
Research Funding: Bristol-Myers Squibb (Inst), Pfizer (Inst), AstraZeneca (Inst), Gilead Sciences (Inst), EMD Serono (Inst), eFFECTOR Therapeutics (Inst)

Robert Dreicer
Consulting or Advisory Role: Astellas Pharma, AstraZeneca, Genentech, Roche, EMD Serono, Incyte, Pfizer, Eisai, Janssen Pharmaceuticals, Modra Pharmaceuticals
Research Funding: Genentech (Inst), Seattle Genetics (Inst), BioClin Therapeutics (Inst), Janssen Pharmaceuticals (Inst), Merck (Inst)

Karim Fizazi
Honoraria: Janssen Pharmaceuticals, Sanofi, Astellas Pharma
Consulting or Advisory Role: Janssen Pharmaceuticals, Bayer AG, Astellas Pharma, Sanofi, Orion Pharma, Curevac, AstraZeneca, ESSA, Roche, Genentech, Amgen
Travel, Accommodations, Expenses: Amgen, Janssen Pharmaceuticals

Silke Gillessen
Honoraria: Janssen Pharmaceuticals
Consulting or Advisory Role: Astellas Pharma (Inst), Curevac (Inst), Novartis (Inst), Active Biotech (Inst), Bristol-Myers Squibb (Inst), Ferring Pharmaceuticals (Inst), MaxiVax, Advanced Accelerator Applications, Roche, Janssen Pharmaceuticals (Inst), Innocrin Pharma (Inst), Sanofi, Bayer AG, Orion Pharma, Clovis Oncology (Inst), Menarini Silicon Biosystems (Inst)
Patents, Royalties, Other Intellectual Property: Method for biomarker (WO 3752009138392 A1)
Other Relationship: Nektar, ProteoMediX

Celeste S. Higano
Employment: CTI (I)
Leadership: CTI (I)
Stock and Other Ownership Interests: CTI (I)
Consulting or Advisory Role: Bayer AG, Ferring Pharmaceuticals, Astellas Pharma, Clovis Oncology, Blue Earth Diagnostics, Myriad Genetics, Tolmar, Janssen Pharmaceuticals, Hinova Pharmaceuticals, Pfizer, AstraZeneca
Research Funding: Aragon Pharmaceuticals (Inst), AstraZeneca (Inst), Dendreon (Inst), Medivation (Inst), Emergent BioSolutions (Inst), Bayer AG (Inst), Pfizer (Inst), Roche (Inst), Astellas Pharma (Inst)
Travel, Accommodations, Expenses: Bayer AG, Astellas Pharma, Clovis Oncology, Blue Earth Diagnostics, Ferring Pharmaceuticals, Menarini, Myriad Genetics, Pfizer, Hinova Pharmaceuticals

Alicia K. Morgans
Honoraria: Genentech, Janssen Pharmaceuticals, Sanofi, AstraZeneca, Astellas Pharma, Astellas Colombia, Bayer AG
Consulting or Advisory Role: Genentech, AstraZeneca, Sanofi, Bayer AG, Astellas Pharma, Janssen Pharmaceuticals
Research Funding: Bayer AG, Seattle Genetics, Astellas Pharma, Genentech, AstraZeneca
Travel, Accommodations, Expenses: Sanofi

Daniel P. Petrylak
Stock and Other Ownership Interests: Bellicum Pharmaceuticals, TYME
Consulting or Advisory Role: Bayer AG, Exelixis, Pfizer, Roche, Astellas Pharma, AstraZeneca, Eli Lilly, Ada Cap, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Clovis Oncology, Incyte, Janssen Pharmaceuticals, Pharmacyclics, Seattle Genetics, Urogen Pharma
Research Funding: Progenics (Inst), Sanofi (Inst), Endocyte (Inst), Genentech (Inst), Merck (Inst), Astellas Pharma (Inst), Medivation (Inst), Novartis (Inst), AstraZeneca (Inst), Bayer AG (Inst), Eli Lilly (Inst), Innocrin Pharma (Inst), MedImmune (Inst), Pfizer (Inst), Roche (Inst), Seattle Genetics (Inst), Clovis Oncology (Inst), Ada Cap (Inst), Bristol-Myers Squibb (Inst)
Expert Testimony: Celgene, Sanofi

Christopher J. Sweeney
Stock and Other Ownership Interests: Leuchemix
Consulting or Advisory Role: Sanofi, Janssen Pharmaceuticals, Astellas Pharma, Bayer AG, Genentech, Roche, AstraZeneca, Pfizer, Amgen, Celgene, Eli Lilly
Research Funding: Janssen Pharmaceuticals (Inst), Astellas Pharma (Inst), Sanofi (Inst), Bayer AG (Inst), Sotio (Inst), Dendreon (Inst)
Patents, Royalties, Other Intellectual Property: Leuchemix, parthenolide, dimethylaminoparthenolide; Exelixis, abiraterone plus cabozantinib combination

Maha Hussain
Honoraria: Onclive, Sanofi, Genzyme, Physicians' Education Resource, Projects in Knowledge, PER, Genentech, Astellas
Consulting or Advisory Role: Pfizer, AstraZeneca, Bayer
Research Funding: Genentech (Inst), Pfizer (Inst), The Prostate Cancer Clinical Trials Consortium (Inst), AstraZeneca (Inst), Bayer (Inst)
Patents, Royalties, Other Intellectual Property: Title: Systems and Methods for Tissue Imaging, 3676. Our file: serial number UM-14437/US-1/PRO 60/923,385, UM-14437/US-2/ORD 12/101,753, US 8,185,186 (US patent number). Systems and methods for tissue imaging (issued patent) EP 08745653.9 (EP application number). Systems and methods for tissue imaging (pending) CA 2683805 (Canadian application number). Systems and methods for tissue imaging (pending) US 13/362,500 (US application number). Systems and methods for tissue imaging (continuation application of US 8,185,186). Title: Method of Treating Cancer. Docket number: serial number 224990/10-016P2/311733 61/481/671. Application filed on May 2, 2011. Title: Dual Inhibition of MET and VEGF for the Treatment of Castration Resistant Prostate Cancer and Osteoblastic Bone Metastases. Applicant/proprietor Exelixis. Application number/patent number 11764665.4-1464. Application number/patent number 11764656.2-1464. Application filed on September 26, 2011
Travel, Accommodations, Expenses: Sanofi, Astellas, Bayer

No other potential conflicts of interest were reported.

JCI The Journal of Clinical Investigation

Molecular profiling stratifies diverse phenotypes of treatment-refractory metastatic castration-resistant prostate cancer

Mark P. Labrecque, … , Peter S. Nelson, Colm Morrissey

J Clin Invest. 2019;129(10):4492-4505. https://doi.org/10.1172/JCI128212.

Research Article | Cell biology | Oncology

Metastatic castration-resistant prostate cancer (mCRPC) is a heterogeneous disease with diverse drivers of disease progression and mechanisms of therapeutic resistance. We conducted deep phenotypic characterization of CRPC metastases and patient-derived xenograft (PDX) lines using whole-genome RNA sequencing, gene set enrichment analysis, and immunohistochemistry. Our analyses revealed 5 mCRPC phenotypes based on the expression of well-characterized androgen receptor (AR) or neuroendocrine (NE) genes: AR-high tumors (ARPC), AR-low tumors (ARLPC), amphicrine tumors composed of cells coexpressing AR and NE genes (AMPC), double-negative tumors (i.e., AR^{-}/NE^{-}; DNPC), and tumors with small cell or NE gene expression without AR activity (SCNPC). RE1 silencing transcription factor (REST) activity, which suppresses NE gene expression, was lost in AMPC and SCNPC PDX models. However, knockdown of REST in cell lines revealed that attenuated REST activity drives the AMPC phenotype but is not sufficient for SCNPC conversion. We also identified a subtype of DNPC tumors with squamous differentiation and generated an encompassing 26-gene transcriptional signature that distinguished the 5 mCRPC phenotypes. Together, our data highlight the central role of AR and REST in classifying treatment-resistant mCRPC phenotypes. These molecular classifications could potentially guide future therapeutic studies and clinical trial design.

Molecular profiling stratifies diverse phenotypes of treatment-refractory metastatic castration-resistant prostate cancer

Mark P. Labrecque,[1] Ilsa M. Coleman,[2,3] Lisha G. Brown,[1] Lawrence D. True,[4] Lori Kollath,[1] Bryce Lakely,[1] Holly M. Nguyen,[1] Yu C. Yang,[2,3] Rui M. Gil da Costa,[2,3] Arja Kaipainen,[2,3] Roger Coleman,[2,3] Celestia S. Higano,[1,5] Evan Y. Yu,[3,5] Heather H. Cheng,[3,5] Elahe A. Mostaghel,[5,6] Bruce Montgomery,[5,6] Michael T. Schweizer,[3,5] Andrew C. Hsieh,[2,3,5] Daniel W. Lin,[1,7] Eva Corey,[1] Peter S. Nelson,[2,3,5] and Colm Morrissey[1]

[1]Department of Urology, University of Washington, Seattle, Washington, USA. [2]Divison of Human Biology and [3]Divison of Clinical Research, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA. [4]Department of Pathology and [5]Department of Medicine, Division of Medical Oncology, University of Washington, Seattle, Washington, USA. [6]Geriatric Research, Education and Clinical Center, Veterans Affairs Puget Sound Health Care System, Seattle, Washington, USA. [7]Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA.

Metastatic castration-resistant prostate cancer (mCRPC) is a heterogeneous disease with diverse drivers of disease progression and mechanisms of therapeutic resistance. We conducted deep phenotypic characterization of CRPC metastases and patient-derived xenograft (PDX) lines using whole-genome RNA sequencing, gene set enrichment analysis, and immunohistochemistry. Our analyses revealed 5 mCRPC phenotypes based on the expression of well-characterized androgen receptor (AR) or neuroendocrine (NE) genes: AR-high tumors (ARPC), AR-low tumors (ARLPC), amphicrine tumors composed of cells coexpressing AR and NE genes (AMPC), double-negative tumors (i.e., AR^-/NE^-; DNPC), and tumors with small cell or NE gene expression without AR activity (SCNPC). RE1 silencing transcription factor (REST) activity, which suppresses NE gene expression, was lost in AMPC and SCNPC PDX models. However, knockdown of REST in cell lines revealed that attenuated REST activity drives the AMPC phenotype but is not sufficient for SCNPC conversion. We also identified a subtype of DNPC tumors with squamous differentiation and generated an encompassing 26-gene transcriptional signature that distinguished the 5 mCRPC phenotypes. Together, our data highlight the central role of AR and REST in classifying treatment-resistant mCRPC phenotypes. These molecular classifications could potentially guide future therapeutic studies and clinical trial design.

Introduction

The androgen receptor (AR) regulates cellular programs that promote the survival and proliferation of prostate cancer (PC) cells. Consequently, first-line treatment for metastatic PC centers on inhibiting AR activity through androgen deprivation therapy (ADT), resulting in the suppression of AR target genes and clinical remissions that generally last several years (1). However, ADT is not curative. PC recurs as castration-resistant prostate cancer (CRPC), typically with reactivated AR signaling. Second-generation AR pathway inhibitors (ARIs), such as enzalutamide (ENZ) and abiraterone (ABI), were designed to further repress AR signaling and are primarily used to treat CRPC. Although these agents extend survival, durable complete responses are rare and these therapies also eventually fail (2, 3).

Typically, the vast majority of metastatic CRPC (mCRPC) tumors progress with rising prostate-specific antigen (PSA/KLK3) levels despite standard of care treatment. Moreover, most mCRPC tumors are adenocarcinomas, which have robust AR program activity (4). Though rigorous epidemiological data are lacking, recent studies report that a substantial number of mCRPC tumors progressing on ARIs have lost AR signaling (5). Paralleling increased use of ARIs has been an increase in the proportion of treatment-resistant CRPC metastases that have AR-null phenotypes, i.e. tumors with diffuse small cell or neuroendocrine (NE) characteristics (SCNPC) or the recently described double-negative (DNPC) phenotype that lacks both NE and AR activity (5). A contemporary study evaluating the histology and molecular characteristics of 202 men with mCRPC found that 17% of the evaluable tumors were classified as SCNPC and this phenotype was associated with short-

Conflict of interest: CSH has been compensated through honoraria from Genentech and as a consultant for Astellas, Bayer, Blue Earth Diagnostics, Clovis Oncology, Ferring, Myriad Genetics, Orion Corporation, Janssen, Hinova, and Tolmar; she has research funding from Aragon Pharmaceuticals, Astellas, AstraZeneca, Bayer, Dendreon, Emergent BioSolutions, Genentech, Medivation, Pfizer, and Roche; she has received travel, accommodation, and expenses from Astellas, Bayer, Blue Earth Diagnostics, Clovis Oncology, Ferring, Genentech, Menarini, Myriad Genetics, Orion Pharma GmbH, Hinova, and Pfizer; she has an immediate family member employed by CTI BioPharma with stock and/or other ownership interests in CTI BioPharma. EYY has been compensated as a consultant for Bayer and Merck and has research support from Agensys, Dendreon, Merck, and Seattle Genetics. HHC has research support from Clovis Oncology, Janssen, Sanofi, and Astellas. BM has research support from Janssen, Beigene, and AstraZeneca. MTS has research support from Janssen, AstraZeneca, Zenith Epigenetics, Pfizer, and Hoffmann-La Roche. ACH has research support from eFFECTOR Inc. EC has research support from Sanofi, AstraZeneca, Gilead, Zenith Epigenetics, Genentech, Janssen, Forma Pharmaceuticals, Bayer, and Abbvie. PSN has been compensated as an advisor to Janssen and has provided expert testimony related to drugs sold by Astellas.

Submitted: February 20, 2019; **Accepted:** July 23, 2019; **Published:** September 16, 2019.
Reference information: *J Clin Invest*. 2019;129(10):4492–4505.
https://doi.org/10.1172/JCI128212.

ened survival (6). Notably, a subset of tumors exhibited discordance between the pathological assessment of SCNPC and gene expression programs. Other tumors exhibited mixed phenotypes of NE features concurrent with AR activity, raising questions of intratumoral heterogeneity due to mixtures of cell types (6).

In addition to histology, the classification of cancers into subtypes with distinct functional features has been supplemented with transcript profiles. For example, transcript signatures subdivide breast cancers into groups that exhibit distinct outcomes (7). This subclassification, based on gene expression levels, has also been applied to localized PC and shown to associate with treatment outcomes (8, 9). In this study, we sought to characterize the phenotypic diversity of treatment-refractory mCRPC using both histological assessments and gene expression profiling. In addition to SCNPC and DNPC, we identified adenocarcinomas that had high AR activity (ARPC), measurable but low AR activity (ARLPC), and amphicrine tumors comprised of cells exhibiting both AR and NE activity (AMPC). Notably, a subset of DNPC tumors exhibited squamous differentiation. We determined that the relationships of 2 major factors regulating cell differentiation states, AR and RE1 silencing transcription factor (REST), associated with these mCRPC subtypes. We generated a 26-gene transcriptional signature that could be clinically useful for classifying mCRPC phenotypes and prioritizing treatment.

Results

Treatment-refractory mCRPC exhibits diverse phenotypes. To assess the diversity of phenotypes present following resistance to therapeutics used to treat metastatic PC, we evaluated 98 tumors obtained at rapid autopsy from 55 men between 2003 and 2017. Patient demographics and clinical data are summarized in Supplemental Table 2; supplemental material available online with this article; https://doi.org/10.1172/JCI128212DS1. All patients received ADT. The median duration of treatment was 4.2 years (range, 0.3–15.1 years). Patients also received a variety of other drugs including docetaxel (n = 44; 80%), abiraterone (n = 8; 15%), enzalutamide (n = 4; 7%) or both abiraterone and enzalutamide (n = 17; 31%). Bone, lymph nodes, and liver were the most frequent sites of metastasis.

To provide an initial evaluation of phenotypic diversity, we used histological assessments and immunohistochemical (IHC) analysis of proteins associated with AR-active adenocarcinomas (AR and PSA) and NE differentiation (chromogranin A, CHGA; synaptophysin, SYP). We observed 5 distinct mCRPC phenotypes: adenocarcinomas with near-uniform expression of AR and PSA, and lack of CHGA and SYP expression, classified as ARPC; adenocarcinomas with weak or heterogeneous expression of AR and PSA, and negative for CHGA and SYP, classified as AR-low PC (ARLPC); tumors composed of cells that coexpress AR, PSA, CHGA, and SYP, classified as amphicrine PC (AMPC); tumors with small cell or neuroendocrine histology with CHGA and SYP expression and lack of AR and PSA expression, classified as small cell or neuroendocrine PC (SCNPC); and tumors lacking detectable expression of AR, PSA, CHGA, and SYP, classified as double-negative PC (DNPC; Figure 1A).

Transcriptome profiles associate with mCRPC phenotypes. Morphologic and IHC analyses are the gold standard for pathologic diagnosis. However, the assessment of transcriptional programs has found utility in subclassifying breast tissue and cancers that exhibit similar histological characteristics (10, 11). We sought to develop a clearer understanding of the mCRPC disease continuum through transcriptome profiling by whole-genome RNA sequencing (RNA-Seq) of 98 mCRPC tumors. Patient metastases were first analyzed and segregated according to expression levels of a gene signature reflecting AR activity (AR panel; Figure 1B). The AR-regulated genes selected for the AR signature are well characterized in the literature and include *KLK3*, *NKX3-1*, *SLC45A3*, and *TARP* (12–14). Tumors were also analyzed and segregated depending on expression levels of NE-associated genes. We previously demonstrated that NE-associated genes can be separated into REST-repressed genes such as *SYP*, *CHGA*, *SNAP25*, and *SRRM4* (NEURO I panel; ref. 15), and transcription factors that regulate NE differentiation, such as *SOX2*, *POU3F2/BRN2*, *NKX2-1*, and *LMO3* (NEURO II panel; refs. 15–17). Applying the AR, NEURO I, and NEURO II gene expression sets to the mCRPC tumors clearly defined the 5 mCRPC subtypes (Figure 1B). ARPC tumors expressed AR-regulated genes but also showed heterogeneity with low expression of some NE genes. ARLPCs had attenuated AR expression with concomitant low expression of some AR-regulated genes. AMPCs expressed AR-associated genes and REST-repressed neuronal factors (NEURO I), but lacked expression of the NE-associated transcription factors (NEURO II). DNPC tumors were generally devoid of AR, NEURO I, and NEURO II panel genes. SCNPC tumors lacked AR expression and signaling but expressed both the NEURO I and NEURO II genes. Analysis of 62 corresponding tumor sites through IHC revealed that phenotypic determinations based on AR, PSA, CHGA, and SYP staining mirrored the phenotypic determinations made through RNA-Seq analysis (Supplemental Figure 1). Moreover, our rapid autopsy cohort included 34 patients, each with 2–3 metastatic sites characterized through RNA-Seq. This provided an opportunity to query the intertumoral phenotypic heterogeneity within patients. Of the 34 patients with 2–3 analyzed metastases, 5 patients (14.7%) displayed phenotypic differences between sites. However, this may underestimate the extent of heterogeneity, as 2–3 metastases generally represent a fraction of the total tumor burden. In addition, there can be intratumoral phenotypic heterogeneity that is not readily assessed through bulk RNA sequencing (Supplemental Figure 2).

To validate the results of the patient specimen analysis using an orthogonal system, we conducted RNA-Seq and IHC analyses on 18 CRPC LuCaP patient-derived xenograft (PDX) lines. The 5 distinct phenotypes were identified by IHC and accurately segregated according to the AR, NEURO I, and NEURO II gene expression profiles (Supplemental Figure 3, A and B).

To discover novel gene expression profiles for each of the mCRPC phenotypes, we cross-compared the patient metastases RNA-Seq data from the defined phenotypic cohorts (i.e., ARLPC, AMPC, DNPC, and SCNPC) relative to ARPC. This analysis generated a comprehensive list of unique and shared upregulated differentially expressed genes (vs. ARPC, up >3-fold and $P < 0.05$; Figure 1C and Supplemental Table 3). In addition, this analysis demonstrated that DNPC and SCNPC are markedly different from the other mCRPC phenotypes (806 and 1669 unique upregulated genes respectively; Figure 1C). Notably, the AR-null phenotypes (DNPC and SCNPC) share an additional 590 upregulated

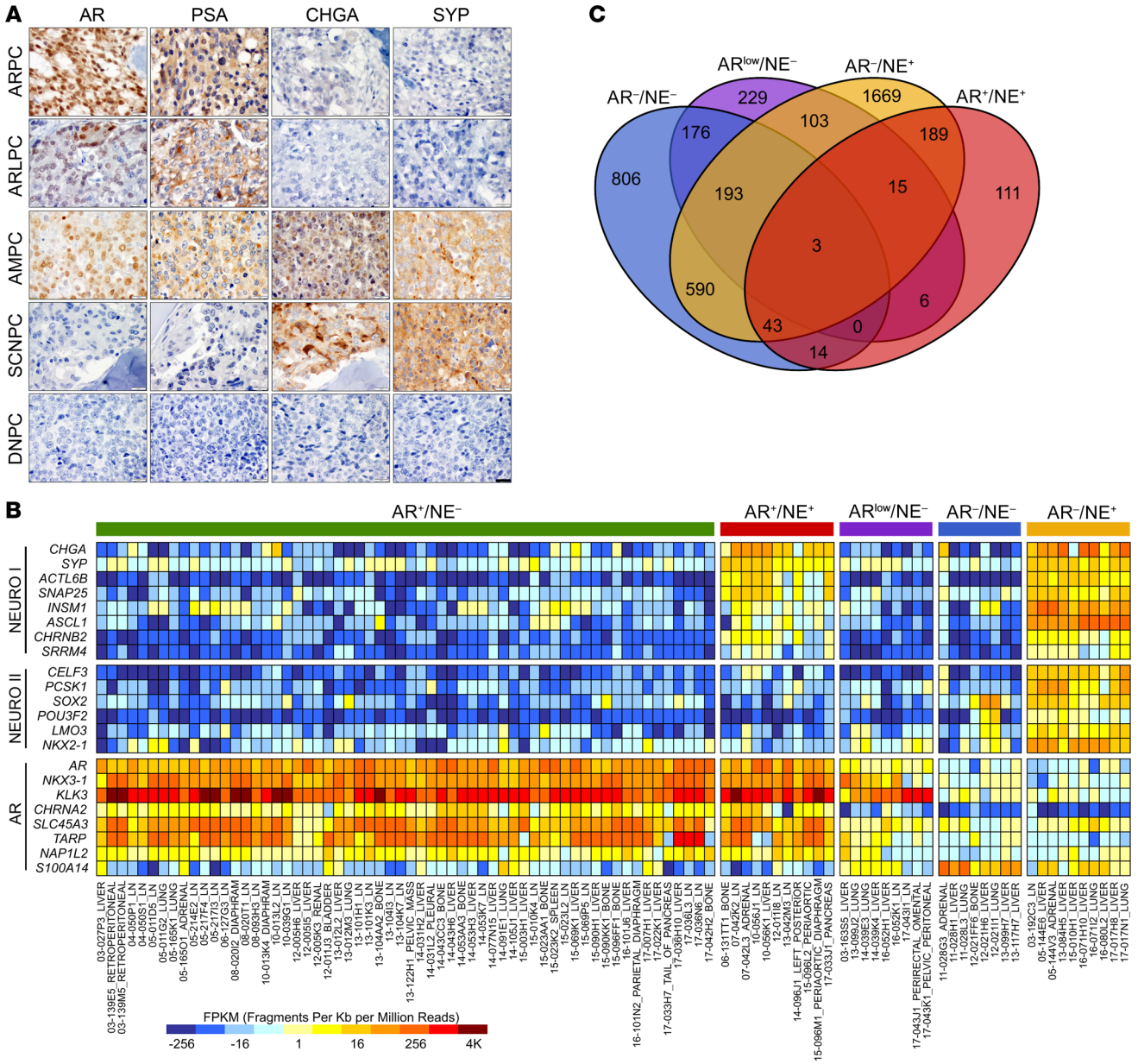


Figure 1. Molecular profiling of mCRPC reveals a heterogeneous disease. (**A**) IHC of 5 mCRPC sites from patients using antibodies to AR, PSA, CHGA, and SYP. Scale bars: 20 μM. (**B**) RNA-Seq heatmap of mCRPC specimens acquired through rapid autopsy from 2003–2017 (n = 98). REST-repressed NE genes are listed in the NEURO I panel (top), NE transcription factors are listed in the NEURO II panel (middle), and AR-associated genes are listed in the AR panel (bottom). Results are expressed as $\log_2$ fragments per kilobase of transcript per million mapped reads (FPKM) and colored according to scale. (**C**) Venn diagram showing the number of unique and shared upregulated genes between phenotypes relative to ARPC (up >3-fold; $P < 0.05$). ARPC (AR-high prostate cancer; AR^+/NE^-), ARLPC (AR-low prostate cancer; AR^{low}/NE^-), AMPC (amphicrine prostate cancer; AR^+/NE^+), DNPC (double-negative prostate cancer; AR^-/NE^-), and SCNPC (small cell or neuroendocrine prostate cancer; AR^-/NE^+).

genes relative to the AR-expressing phenotypes (Figure 1C). Furthermore, ARLPC, and AMPC share gene expression profiles similar to ARPC (Figure 1C).

Gene Set Enrichment Analysis (GSEA) determined that the 806 upregulated genes unique to DNPC were enriched in Gene Ontology biological process terms for response to external biotic stimulus ($P = 4.5 \times 10^{-18}$), immune system process ($P = 3.5 \times 10^{-15}$), and cornification ($P = 5.5 \times 10^{-9}$). As expected, the 1669 upregulated genes unique to SCNPC were enriched for core neuronal activities such as nervous system process ($P = 7.5 \times 10^{-12}$) and regulation of nervous system process ($P = 4.7 \times 10^{-10}$). Interestingly, the top processes for the 829 upregulated genes in common between SCNPC and DNPC included locomotory behavior ($P = 5.0 \times 10^{-07}$) and cell adhesion ($P = 2.1 \times 10^{-07}$), suggesting changes in metastatic potential common to AR-null phenotypes. The 229 upregulated genes unique to the ARLPC phenotype were enriched for processes in response to external biotic stimulus ($P = 3.3 \times 10^{-07}$) and regulation of inflammatory response ($P = 8.4 \times 10^{-06}$), while the 193 upregulated genes in common between ARLPC, DNPC, and SCNPC phenotypes were significantly enriched in acute inflammatory

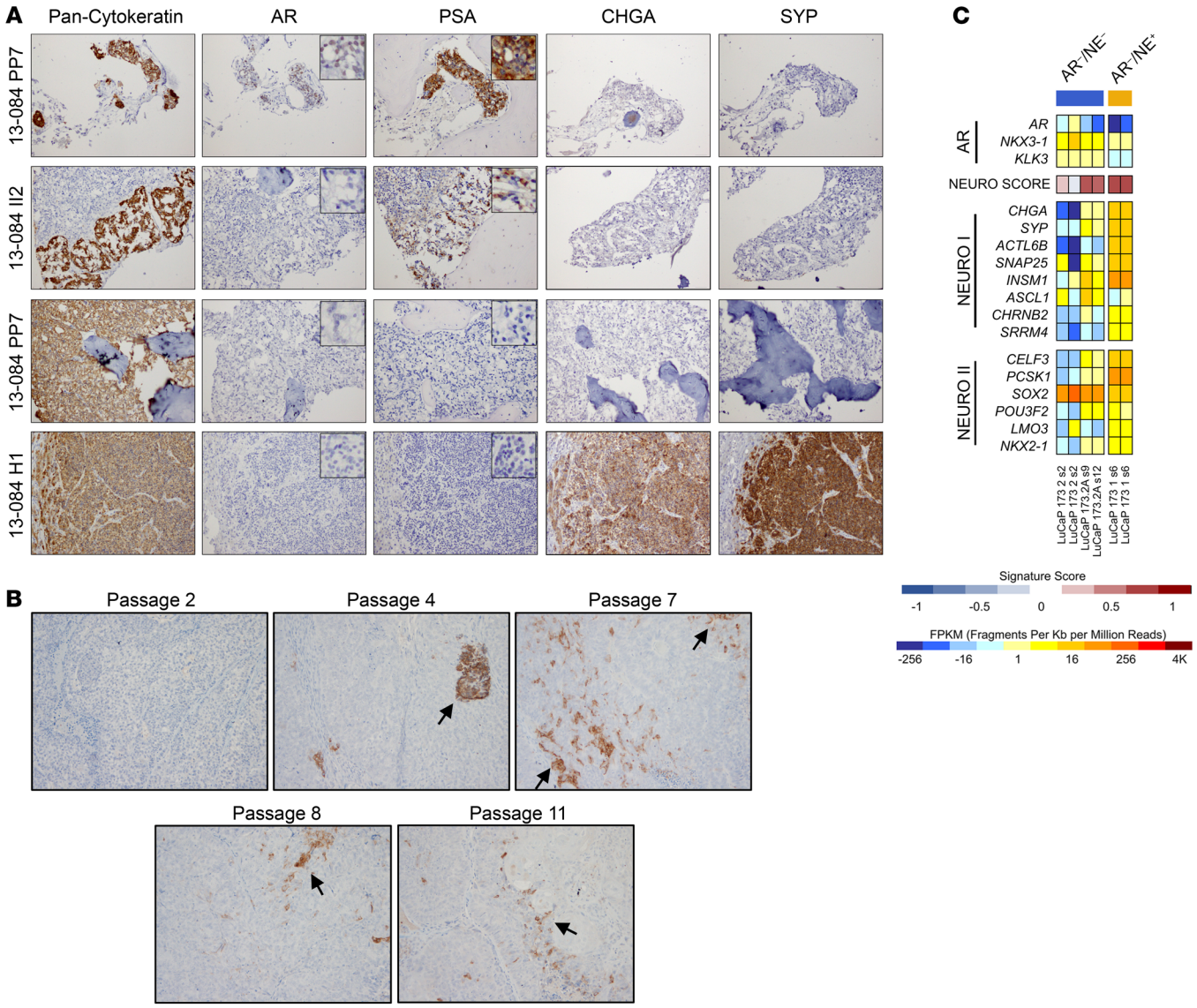


Figure 2. Disease progression is a continuum in mCRPC specimens. (**A**) IHC of different mCRPC sites from patient 13-084. Site PP7 (bone; ARPC), II2 (bone; ARLPC), PP7 (bone; DNPC), and H1 (liver, SCNPC). Primary antibodies were directed toward pan-cytokeratin, AR, PSA, CHGA, and SYP. Insets for AR and PSA staining are images of the same section using the ×400 objective lens. Original magnification 40×. (**B**) IHC of LuCaP 173.2 tumor sections from passages 2, 4, 7, 8, and 11 using a SYP antibody. Black arrows point to clusters of cells with SYP positivity. Magnification 100×. (**C**) RNA-Seq heatmap and NEURO score of LuCaP 173.1 and serial passages from LuCaP 173.2. Results are expressed as $\log_2$ FPKM or as enrichment scores and are colored according to scale.

response ($P = 4.0 \times 10^{-11}$) and defense response ($P = 1.3 \times 10^{-06}$). Finally, GSEA determined that the 111 upregulated genes unique to AMPC were not involved in any significant processes. However, the 250 common upregulated genes between AMPC and SCNPC were involved in ancillary neuronal processes such as neurotransmitter transport ($P = 4.4 \times 10^{-10}$) and synaptic vesicle localization ($P = 6.5 \times 10^{-09}$). Importantly, analysis of the 250 significantly upregulated genes shared between SCNPC and AMPC using the MSigDB C3-Transcription Factor Target database showed that REST was the top transcription factor pathway altered in the gene set ($P = 4.2 \times 10^{-35}$; Supplemental Table 4). Taken together, these data support the use of AR, NEURO I, and NEURO II genes to segregate mCRPC phenotypes and identify biologically relevant pathways that emphasize the heterogeneity of mCRPC.

mCRPC phenotypes represent a disease continuum. The relationships between different mCRPC phenotypes have not been clearly established though prior studies suggest that SCNPC is often derived from an AR-positive precursor, or share a common progenitor (18, 19). Thus, we investigated these relationships by studying the phenotypic progression of an individual with mCRPC and a complicated treatment history. At diagnosis in 2012, patient 13-084 had a PSA of 159 ng/mL and a prostate biopsy revealed an adenocarcinoma with a Gleason score of 4 + 5 = 9 and IHC demonstrating focal NE differentiation. He was treated with leuprolide and bicalutamide but ensuing CT and bone scans revealed numerous metastases in liver, lung, and bone. Platinum-based chemotherapy was initiated due to the possible presence of SCNPC with cycles of carboplatin/irinotecan (5 cycles) or cisplatin/irinotecan

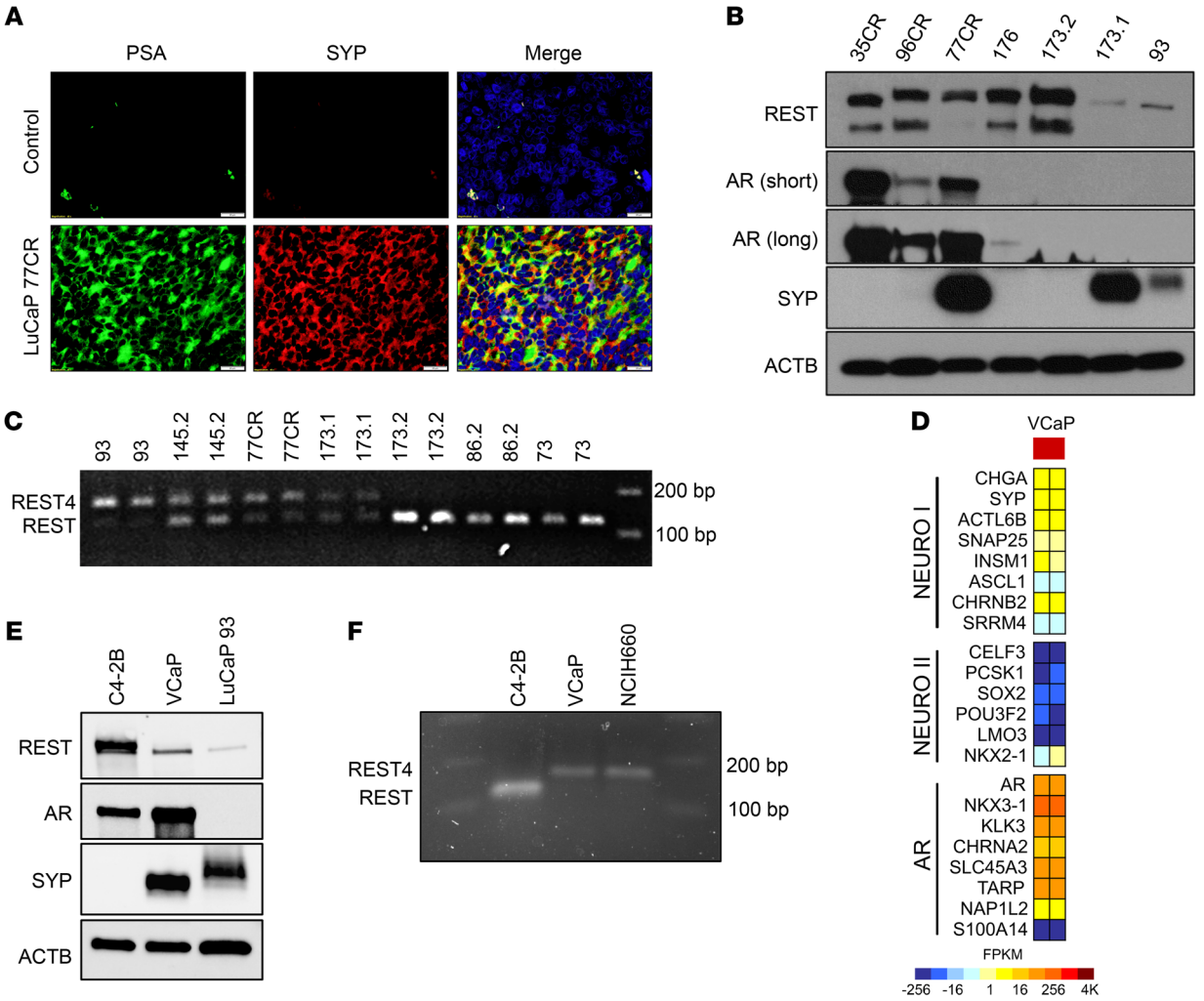


Figure 3. REST splicing occurs in AMPC and SCNPC phenotypes. (**A**) Immunofluorescence of an AMPC LuCaP 77CR tumor using PSA (green) and SYP (red) antibodies. Sections were counterstained with DAPI (blue) and top panels represent LuCaP 77CR PDX sections stained with secondary antibody only. Scale bars: 20 μM. (**B**) Immunoblot of LuCaP PDX specimens probing for REST, AR, and SYP. ACTB was used as a loading control. Short, 10-second film exposure; long, 5-minute film exposure. (**C**) PCR of LuCaP PDX specimens using primers specific to REST shows the REST4 insertion sequence appearing in AMPC (LuCaP 77CR) and SCNPC (LuCaP 93, 145.2, and 173.1) but not in DNPC (LuCaP 173.2) or ARPC (LuCaP 86.2 and 73). (**D**) RNA-Seq heatmap of VCaP cells displaying NE-associated genes (NEURO I and NEURO II) and AR-associated genes. Results are expressed as $\log_2$ FPKM and colored according to scale. (**E**) Immunoblot of C4-2B, VCaP, and LuCaP 93 whole-cell extracts using antibodies against AR, REST, SYP, and ACTB. ACTB was used as a loading control. (**F**) PCR of C4-2B, VCaP, and NCIH660 cells using primers specific to REST. The upper band represents the REST4 splice variant.

(3 cycles) leading to a PSA decline and stable disease for approximately 8 months. He subsequently received 2 cycles of capecitabine and gemcitabine with eventual PSA progression prior to death (Supplemental Figure 4). At autopsy in 2013, we recovered several metastatic tumors that exhibited different phenotypes, including ARPC, ARLPC, and DNPC sites in bone and SCNPC sites in the liver as determined by IHC (Figure 2A). We developed 2 PDX lines representing SCNPC (LuCaP 173.1) and DNPC (LuCaP 173.2) from acquired patient metastases (5). Previous reports have described the transdifferentiation of an AR-expressing adenocarcinoma PC PDX line to SCNPC (20). We therefore questioned whether the DNPC phenotype is a transition stage. We sought to test the hypothesis that sustained tumor growth through serial passaging of the DNPC LuCaP 173.2 PDX line would lead to SCNPC conversion. Indeed, serial passaging in intact mice of LuCaP 173.2 and staining for SYP expression through IHC showed that first passage PDX tumors were negative for SYP expression, whereas SYP-positive cells were detected by passage 4 and were maintained as a minor cell population through passage 9 (Figure 2B). RNA-Seq of LuCaP 173.2 from passages 2, 9, and 12 indicated that the NEURO I and NEURO II panels of genes were expressed at substantially higher levels in the later passages (Figure 2C). Furthermore, the NEURO scores of LuCaP 173.2 from passages 9 and 12 were similar to SCNPC LuCaP 173.1. These data suggest that mCRPC is a disease continuum, and that although the DNPC phenotype is generally stable, a small proportion of DNPC tumor cells possess an intrinsic plasticity that permits conversion to SCNPC.

The amphicrine phenotype and relationship with REST expression. Historically, SCNPC was considered to lack AR activity but recent studies have identified atypical tumors with NE features that express

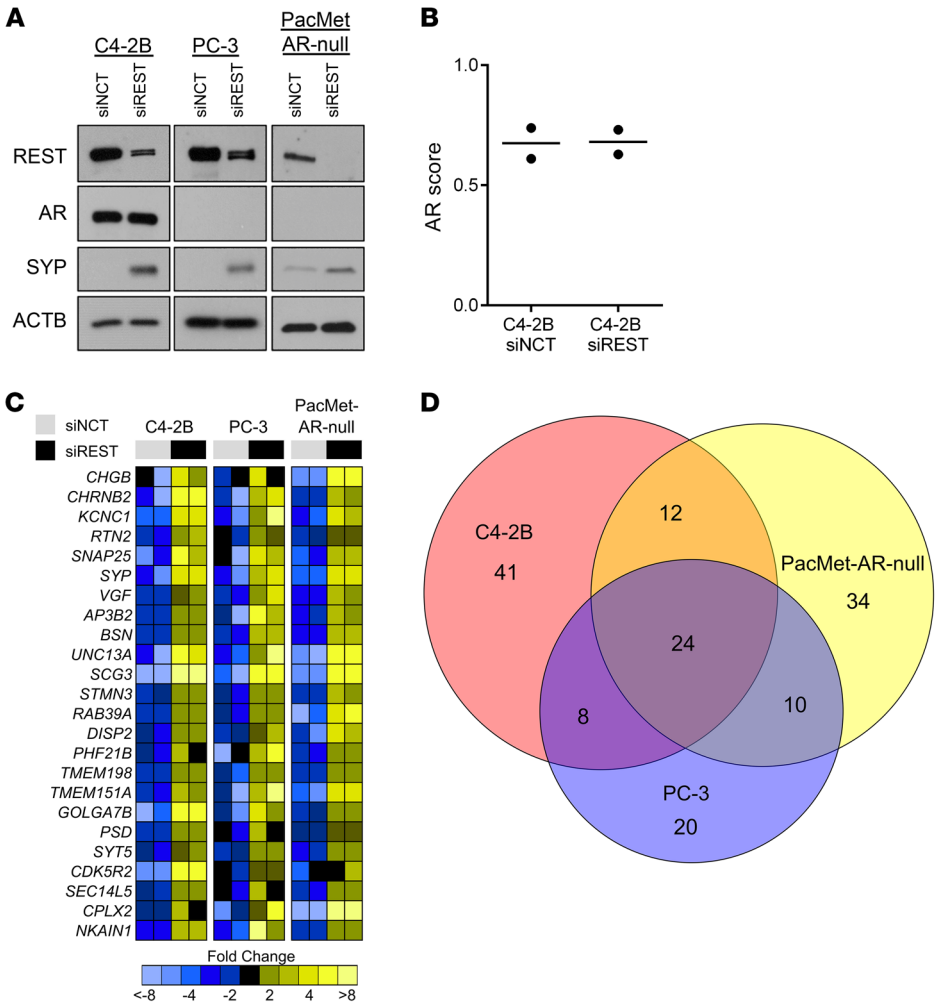


Figure 4. REST knockdown in AR-expressing and AR-null CRPC cell lines. (**A**) Immunoblot of REST, AR, SYP, and ACTB using C4-2B, PC-3, and PacMet AR-null cells transfected with either REST siRNA (siREST) or negative control siRNA (siNCT). (**B**) AR activity scores assessed in C4-2B cells transfected with siNCT ($n = 2$) or siREST ($n = 2$) by RNA-Seq. (**C**) RNA-Seq heatmap of the 24 common upregulated genes (up >3-fold; $P < 0.05$) between C4-2B, PC-3, and PacMet AR-null cells transfected with siREST or siNCT. Log_2 mean-centered ratios of genes are depicted and colored according to scale. (**D**) Venn diagram describing the interrelationships of all upregulated genes (vs. siNCT; up >3-fold; $P < 0.05$) identified through RNA-Seq in siREST transfected cell lines.

AR and exhibit AR-mediated signaling (6). In addition, classification of the AMPC phenotype based on bulk RNA-Seq or IHC using single markers may be due to tumors comprised of multiple cell types (AR^+/NE^- and AR^-/NE^+) or may be due to tumors comprised of individual cells expressing both AR and NE differentiation markers simultaneously. Thus, to establish the existence of AMPC cells in our clinical specimens (i.e., cells with both AR transcriptional output and neuroendocrine features; AR^+/NE^+), we stained LuCaP PDX tumors and patient metastases with immunofluorescent (IF) antibodies to PSA and SYP. AMPC LuCaP 77CR tumors contained numerous cells coexpressing PSA and SYP (Figure 3A). Though PSA and SYP coexpression normally occurred throughout LuCaP 77CR tumors, we also identified a subset of tumors with focal SYP expression (unpublished observations). Furthermore, we used IF to characterize 6 AMPC metastases from 4 patients. The patient tissues used for IF analysis were adjacent to the specimens used for RNA-Seq. Importantly, IF demonstrated clear PSA and SYP coexpression in patient tumor cells. However, patient 13-042 site M3 and patient 17-033 site J1 showed regions that were mixed of distinct populations of ARPC and SCNPC tumor cells (Supplemental Figure 5).

Previously, we interrogated SCNPC patient tumors and PDX lines and determined that SCNPC is associated with loss of REST repressor activity (15). However, the role of REST in other mCRPC phenotypes has not been evaluated. Using representative PDX lines from ARPC (LuCaP 35CR and 96CR), AMPC (LuCaP 77CR), ARLPC (LuCaP 176), DNPC (LuCaP 173.2), and SCNPC (LuCaP 173.1 and 93), we found that full-length REST protein was decreased in both AMPC and SCNPC tumors (Figure 3B). Interestingly, we observed REST species with our REST C-terminus antibody at both approximately 120 KDa and approximately 200 KDa in PDX lysates from ARPC, ARLPC, and DNPC. Full-length REST protein is predicted to be 116 KDa but can be O-glycosylated and readily detected at approximately 200 KDa (21, 22). Additionally, the REST transcript has multiple splice variants that produce truncated proteins (23). Nevertheless, both REST proteins with intact C-terminus repressor domains were diminished in AMPC and SCNPC PDX models. Moreover, AMPC LuCaP 77CR showed robust expression of both AR and SYP protein, whereas ARLPC LuCaP 176 had low AR protein expression (Figure 3B).

Next, we examined alternative splicing of the REST transcript. The RNA splicing factor SRRM4 splices the REST transcript to REST4, resulting in the loss of the C-terminus repressor domain and diminished REST transcriptional repression (15, 24, 25). To examine SRRM4-mediated splicing of REST in mCRPC phenotypes, we conducted PCR using REST primers spanning the SRRM4 splice site and determined that REST4 splicing events occurred exclusively in AMPC and SCNPC LuCaP PDX models (Figure 3C). However, instead of a previously reported 62 bp inser-

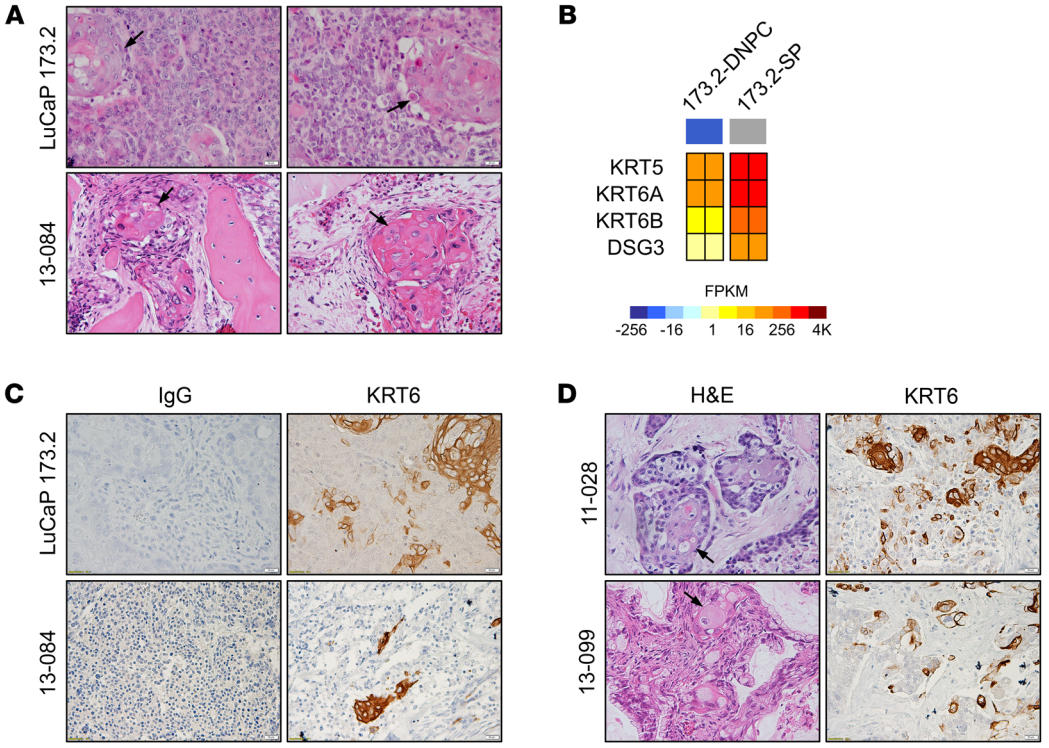


Figure 5. DNPC can convert to a squamous phenotype. (**A**) H&E staining of mCRPC tissues from LuCaP 173.2 and patient 13-084. Black arrows point to squamous pearl structures. (**B**) Expression of squamous cell lung cancer associated genes from RNA-Seq of LuCaP 173.2 DNPC cells and squamous pearl (SP) cells isolated by laser capture microdissection. Results are expressed as $\log_2$ FPKM and colored according to scale. (**C**) IHC of specimens from LuCaP 173.2 and patient 13-084 using KRT6 antibody or IgG as a negative control. (**D**) H&E staining (left panels) and KRT6 IHC (right panels) of DNPC tumor sections from patients 11-028 and 13-099. Scale bars: 20 μM.

tion into the REST transcript (25), band sequencing identified a 50 bp insertion, suggesting a mechanism of REST4 splicing in AMPC and SCNPC phenotypes similar to small cell lung cancer (26). Taken together, these data indicate that the AMPC phenotype arises from the loss of REST transcriptional repression.

To further support the existence of the AMPC phenotype, we interrogated the VCaP PC cell line, which exhibits an amphicrine-like transcript profile. RNA-Seq confirmed that VCaP cells express AR-associated genes and the REST-repressed NEURO I genes but do not express the NEURO II transcription factors that drive the SCNPC phenotype (Figure 3D). Immunoblot analysis determined that VCaP cells express considerable AR and SYP protein and have diminished full-length REST protein expression compared with C4-2B cells (Figure 3E). Immunofluorescence validated that both PSA and SYP are coexpressed in the same VCaP cell (Supplemental Figure 6) and PCR analysis of REST determined that REST transcripts are alternatively spliced to REST4, similar to neuroendocrine NCIH660 cells (Figure 3F). Notably, the growth of VCaP cells is inhibited by ADT or exposure to the AR antagonist enzalutamide (27). In addition, 22Rv1 cells also exhibit features of AMPC as they have attenuated REST expression and appreciable SYP and AR protein expression (28). Taken together, these results confirm the existence of AMPC cells in patient specimens and in CRPC models in vitro and in vivo, and suggest that the AMPC phenotype is still driven by AR activity and is responsive, at least transiently, to AR pathway repression.

REST knockdown in CRPC cells promotes an amphicrine phenotype. To examine the impact of the loss of REST activity in AR-expressing and AR-null cell lines, we conducted knockdown studies using siRNAs directed to REST (siREST) or a negative control (siNCT) in C4-2B, PC-3, and PacMet AR-null cells. PacMetUT1 cells were modified using CRISPR-Cas9–mediated editing to knockout AR expression and were characterized previously (5, 29). REST knockdown led to increases in the NE-associated protein SYP (Figure 4A). Interestingly, REST depletion in AR-expressing C4-2B cells did not alter AR protein expression or the magnitude of AR transcriptional output (Figure 4, A and B). However, this does not rule out the possibility that complete loss of REST could alter the AR transcriptional output. Transcript profiling by RNA-Seq and subsequent GSEA showed that REST ablation in C4-2B, PC-3, and PacMet AR-null cells led to significant upregulation of known REST-repressed genes (up >3-fold; $P < 0.05$). Furthermore, the REST pathway was the top altered pathway from the MSigDB C3-Transcription Factor Target database in all siREST transfected cell lines. Surprisingly, the number of genes significantly upregulated with REST knockdown was relatively low across all cell models and only 24 genes were in common between C4-2B, PC-3, and PacMet AR-null cells (Figure 4, C and D; Supplemental Table 5). The REST-repressed genes with increased expression following REST depletion included *SYP, SNAP25, CHRNB2* (NEURO I Panel) as well as *VGF*, *SCG3*, and *CHGB* (Figure 4C). However, REST knockdown did not significantly alter the expression of transcrip-

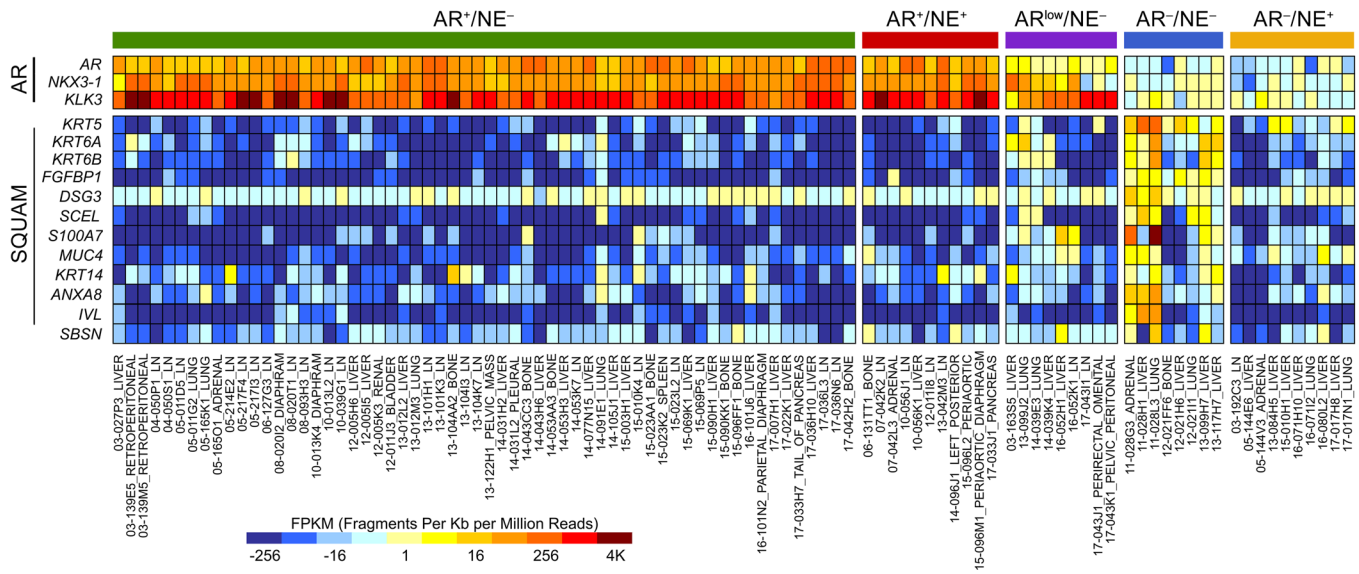


Figure 6. Expression of squamous markers is associated with DNPC and ARLPC. RNA-Seq heatmap of patient specimens (n = 98) highlighting AR-regulated genes and genes associated with squamous pearl cells (SQUAM). Results are expressed as $\log_2$ FPKM and colored according to scale.

tion factors and drivers of SCNPC such as *NKX2-1*, *POU3F2*, and *SOX2* (NEURO II panel) in either AR-expressing or AR-null CRPC cell lines (Supplemental Figure 7). Taken together, we determined that REST loss induces the expression of a limited set of NE-associated genes (NEURO I) and drives PC conversion to the AMPC phenotype with continued evidence of AR activity.

A subtype of mCRPC exhibits features of squamous cell carcinoma. While histologically characterizing the DNPC LuCaP 173.2 PDX model, we observed squamous pearls, which were evidence of focal squamous differentiation (Figure 5A). To determine if the squamous pearls occurred spontaneously during LuCaP 173.2 development or were native to the original malignancy, we evaluated tumors from patient 13-084 and identified squamous pearl structures in adjacent tumor sections of the rib bone metastasis that served as the origin of LuCaP 173.2 (Figure 5A). Squamous pearl cells from LuCaP 173.2 PDX tumors were then isolated using laser capture microdissection and subjected to RNA-Seq and GSEA. Transcriptome analysis determined that 880 genes were upregulated and 29 genes were downregulated in LuCaP 173.2 squamous pearl cells compared with surrounding DNPC tumor cells (FDR < 0.001; Supplemental Table 6). GSEA determined that many of the upregulated genes were enriched in other squamous cancer gene sets, such as RICKMAN_HEAD_AND_NECK (P < 0.0001; ref. 30). Importantly, KRT5, KRT6A, KRT6B, and DSG3 were recently highlighted through ROC curves as biomarkers to differentiate lung adenocarcinoma from lung squamous cell cancer (31). Indeed, our analysis showed that *KRT5*, *KRT6A*, *KRT6B*, and *DSG3* were highly expressed in LuCaP 173.2 squamous pearl cells compared with surrounding DNPC tissue (Figure 5B). IHC using a primary antibody specific to KRT6 in LuCaP 173.2 and 13-084 tumor specimens revealed strong KRT6 staining only in tumor cells with squamous pearl morphology (Figure 5C).

Examination of 4 other patients with DNPC metastases identified squamous pearls with positive KRT6 staining in 2 patients: 11-028 and 13-099 (Figure 5D). Interestingly, patient 11-028 had an adenocarcinoma phenotype in the initial prostate biopsy and was subsequently treated with diethylstilbesterol (DES) for 13 months prior to cystoprostatectomy. At the time of cystoprostatectomy, histology and IHC revealed adenocarcinoma with focal basaloid and squamous differentiation in several sections of the prostate as well as a left axillary lymph node that was consistent with squamous carcinoma. The other 2 patients with KRT6-positive metastases, patients 13-084 and 13-099, had primary prostate cancers with no evidence of squamous differentiation, and subsequent hormone therapy led to the appearance of squamous mCRPC. Although DES and hormone therapies have been linked to the development of squamous cancer in the prostate with subsequent squamous metastases (32–36), this report provides evidence for hormone therapy–mediated conversion of ARPC to squamous DNPC at metastatic sites.

We compared the top significantly (FDR < 0.001) upregulated genes from the LuCaP 173.2 squamous pearl data set with the literature to identify genes with known roles in squamous cell differentiation or other squamous cancers. In addition to *KRT5*, *KRT6A*, *KRT6B*, and *DSG3*, we also found *IVL*, *SBSN*, *FGFBP1*, *SCEL*, *S100A7*, *MUC4*, *KRT14*, and *ANXA8* to be significantly overexpressed in other squamous cell types (37–44). Importantly, RNA-Seq heatmaps show that these genes are strikingly elevated in subsets of both ARLPC and DNPC patient specimens (Figure 6), suggesting that ARLPC and DNPC phenotypes could be transition states to squamous mCRPC. These results indicate that squamous cell conversion is not a rare occurrence in end-stage disease and should be considered an emerging phenotype following resistance to AR-directed therapy.

Transcript signatures define the molecular phenotypes of mCRPC. The variability in expression of any single marker, both at the biological level and technical level makes tumor classification by immunohistochemistry challenging. Transcript panels for tumor

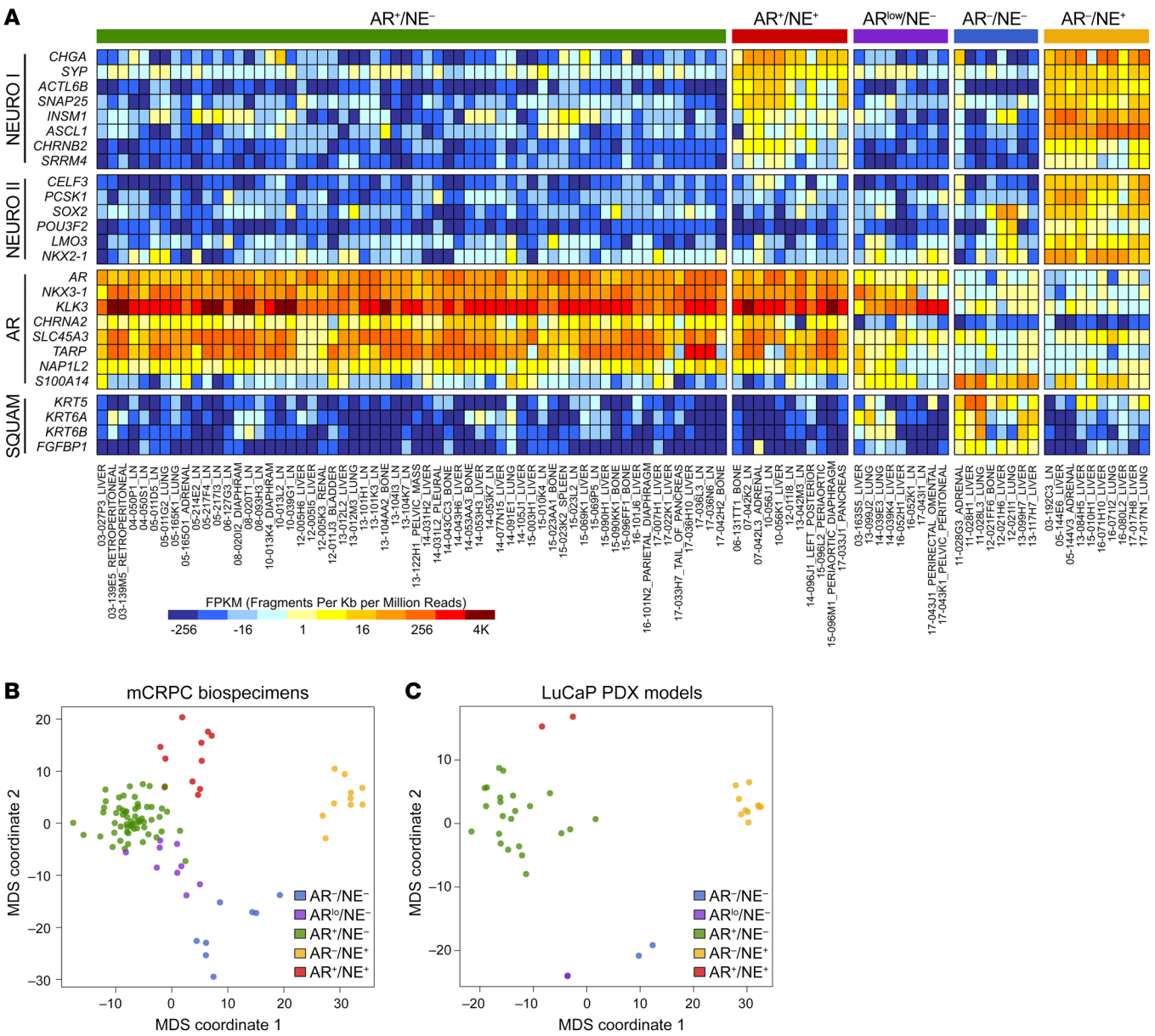


Figure 7. Cluster analysis using AR, NE, and squamous gene expression profiles segregates mCRPC specimens and LuCaP PDX models into the different phenotypes. (**A**) RNA sequencing of mCRPC specimens acquired between 2003–2017 (n = 98; modified from Figure 1B). NE genes listed in the NEURO I and NEURO II panels, AR and AR-regulated genes are listed in the AR panel, and squamous associated genes are shown in SQUAM panel. Results are expressed as $\log_2$ FPKM and colored according to scale. Multidimensional scaling and cluster analysis of (**B**) mCRPC specimens (n = 98) and (**C**) LuCaP PDX models using the 26-gene set depicted in A. The LuCaP analysis was conducted on 18 distinct PDX lines (n = 2 for each line). ARPC (AR^+/NE^-; green), ARLPC (AR^{low}/NE^-; purple), DNPC (AR^-/NE^-; blue), AMPC/mixed (AR^+/NE^+; red), SCNPC (AR^-/NE^+; yellow).

classification have been explored as predictive and prognostic biomarkers for treatment decision-making (45, 46). We leveraged the data generated from the patient metastases and LuCaP PDX models to develop a 26-gene transcriptomic signature for defining treatment-refractory mCRPC phenotypes. Using the aforementioned AR, NEURO I, and NEURO II gene panels, as well as a squamous panel (SQUAM) that includes *KRT5*, *KRT6A*, *KRT6B*, and *FGFBP1*, we conducted multidimensional scaling (MDS) and cluster analysis of the patient metastases and LuCaP PDX models (Figure 7A and Supplemental Figure 3B). The MDS demonstrated clear distinction between the 5 mCRPC phenotypes (ARPC, ARLPC, AMPC, DNPC, and SCNPC) in both patient specimens and LuCaP PDX models (Figure 7, B and C).

We further evaluated our 26-gene signature using PolyA RNA-Seq landscapes from 270 CRPC metastases in the Stand Up To Cancer (SU2C) data set (47). Although the SU2C data set contains RNA-Seq from mCRPC tumors earlier in disease progression and from tumors that are responding to treatment, the transcriptional signature segregated the tumors into the 5 mCRPC phenotypes (Supplemental Figure 8, A and B). Interestingly, we detected expression of the squamous-associated genes in 2 DNPC tumors and 2 ARLPC tumors but also observed marked squamous marker

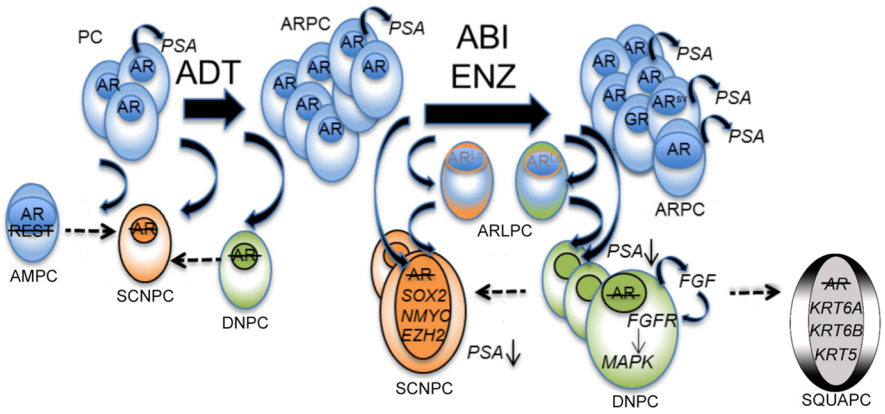


Figure 8. Schematic of the mCRPC disease continuum. The proposed mechanisms, molecular drivers, and cellular differentiation states following AR pathway inhibition therapy. ADT, androgen deprivation therapy; ABI, abiraterone; ENZ, enzalutamide; PC, hormone-sensitive prostate cancer; ARPC, AR-high prostate cancer; ARLPC, AR-low prostate cancer; SCNPC, small cell or NE prostate cancer; DNPC, double-negative prostate cancer; AMPC, amphicrine prostate cancer; SQUAPC, squamous prostate cancer.

expression in 4 ARPC tumors and 1 SCNPC tumor. Thus, removing the squamous genes from the analysis showed a more effective clustering of the tumors into their respective phenotypes (Supplemental Figure 8C). We do not know if the ARPC and SCNPC specimens with squamous aspects represent tumors containing 2 different phenotypes or single phenotypes.

Discussion

The clinical phenotyping of mCRPC has been limited to morphologic and immunohistochemical analyses. Although adenocarcinoma (AR and PSA) and NE (CHGA and SYP) biomarkers have provided some clarity for pathologic classification, the complexity of tumor heterogeneity, and the emergence of new treatment-resistant phenotypes have catalyzed a need for deeper understanding of the mCRPC disease continuum. Moreover, anaplastic tumors or aggressive variants are a clinically defined group of small cell metastatic/CRPC phenotypes with varying degrees of both AR expression (generally AR-null) and NE differentiation (48, 49). The classifications prompted a call for further elucidation of underlying mCRPC biology and more accurate nomenclature that limits confusion between research and medical fields (50). At the transcriptome level, expression signatures for classifying SCNPC have been demonstrated (51), but an encompassing signature that appreciates the spectrum of mCRPC phenotypes has not been identified. In this report, we interrogated end-stage mCRPC patient specimens and treatment-resistant LuCaP PDX models and demonstrated that transcriptome analysis in conjunction with IHC is a powerful method for phenotyping mCRPC in the current era. Our approach led to the characterization of 5 distinct mCRPC phenotypes (AR-high/ARPC, AR-low/ARLPC, amphicrine/AMPC, double-negative/DNPC, and small cell or NE tumors lacking AR expression/SCNPC) and ultimately resulted in a clinically relevant 26-gene transcriptional signature to classify mCRPC biospecimens. Moreover, our data demonstrated that mCRPC is a disease continuum driven by AR, REST, and core SCNPC transcription factor programs; treatment-induced differentiation of DNPC to squamous cell carcinoma is an emerging mCRPC phenotype; AR-low and AR-null phenotypes share common pathways of resistance to AR pathway inhibition that could be exploited for clinical benefit; and loss of REST repressor activity is critical for driving conversion to the AMPC/mixed phenotype but only promotes rather than drives the SCNPC phenotype.

Observations made through our rapid autopsy program support a treatment-induced shift in mCRPC phenotypes with ARI therapies increasing the number of AR-null and AR-low metastases at end-stage disease (5). In addition, our patient, LuCaP PDX, and cell line data suggest that ARPC can transition to ARLPC, AMPC/mixed, DNPC/squamous, or SCNPC to bypass hormone or AR pathway suppression therapies. These results were further verified through our analysis of the SU2C cohort of CRPC metastases (47). Notably, DNPC is a proliferative AR-null intermediate that contains cells with the inherent plasticity and potential to convert to SCNPC or squamous mCRPC (Figure 8 and Supplemental Figure 9). Multiple cell line, murine model, and PDX reports have demonstrated that loss of tumor suppressor proteins, AR-directed therapies, and/or the tumor microenvironment contribute to CRPC cellular plasticity and ARPC to SCNPC transition (16, 20, 52–56). Moreover, Beltran et al. have established that subsets of NE tumors are clonally derived from ARPC (18). Of note, the genomic landscapes of intrapatient CRPC metastases are relatively similar (4). Thus, our analysis indicating that intertumoral phenotypic heterogeneity is not a rare occurrence argues that epigenetic, posttranscriptional, posttranslational, and microenvironment events can contribute to phenotypic diversity in mCRPC. Taken together, our data add further clinical support for the proposed mCRPC disease continuum and demonstrates that treatment-induced selective pressures can change the phenotypic and molecular landscapes of mCRPC.

The analyses of DNPC tumors and the LuCaP 173.2 PDX model unexpectedly revealed the appearance of squamous cell pearls within the mass of DNPC tumor cells. RNA-Seq and staining for KRT6 confirmed the molecular nature of the squamous pearls. We hypothesize that only the most differentiated squamous carcinoma cells stain positive for KRT6 and display a cornified GSEA profile and that there exists a proliferating DNPC/squamous intermediary. Support for this hypothesis comes from RNA-Seq and IHC that shows ARLPC metastases and LuCaP 176 significantly enriched for squamous transcriptional profiles but negative for squamous pearl structures and KRT6 staining. The mechanisms of ARLPC/DNPC to squamous transition remain unclear, but future research examining the parallels between prostate and lung cancer lineage plasticity is warranted. For example, prostate and lung epithelial cells can be reprogrammed to small cell NE cancers through induction of the same transcription factor pathways (19). Moreover, lung ade-

nocarcinomas can transition to squamous cell carcinomas through *LKB1*-loss (57). Our RNA-Seq data show no evidence *LKB1/STK11*-loss across patient samples but other mechanisms of adenocarcinoma-squamous differentiation are likely. We speculate that there are common molecular pathways driving lung and prostate cancer lineage switching. Taken together, our data demonstrate that treatment-induced ARPC-DNPC-squamous conversion is one potential pathway to bypass AR-suppression strategies.

There are currently no standard treatments for SCNPC, DNPC, and ARLPC phenotypes. However, RNA-Seq and GSEA between mCRPC phenotypes revealed biologically relevant pathways that could be further interrogated for therapeutic benefit. Significantly upregulated genes common to the AR-null and ARLPC phenotypes were enriched for cell adhesion processes, and delving into the pathway revealed *CEACAM5* as a top hit. CEACAM5 has been identified as a surface marker of potential utility in directing chimeric antigen T cells in SCNPC (58), and our data reveal that this therapy could also be clinically effective against subsets of ARLPC and DNPC tumors. Moreover, upregulated genes common to ARLPC and AR-null phenotypes are enriched in immune system, inflammatory, and defense responses. Since the phenotype comparisons were relative to ARPC, these data support the notion that the immune cell content of ARLPC and AR-null tumors is strikingly different from that of ARPC tumors. Notably, DNPC-specific immune-related genes included *IL8* and *CXCR1*, which have been reported to promote CRPC metastasis and angiogenesis (59), and genes such as *TGFB* and *RUNX2*, which support tumor growth in bone (60). Whether associated with the tumor cells, immune cells, or stromal cells, the presence of enriched immunomodulatory signaling pathways suggests that ARLPC, DNPC, and SCNPC tumors could be more receptive to immunotherapies.

Our group and others have previously demonstrated that loss of REST repressor activity promotes the SCNPC phenotype (15, 24, 61, 62). Here, we confirmed the existence of AMPC cells in vivo and in vitro and demonstrated that AMPC cells express a limited set of neuronal genes that are REST-repressed (NEURO I panel) and maintain AR signaling. Furthermore, transcriptome analysis of mCRPC and LuCaP PDX tumors and siRNA-mediated knockdown of REST in AR-expressing and AR-null cell lines provided compelling evidence that loss of REST repressor activity is critical for conversion to the AMPC/mixed phenotype but does not necessarily drive the SCNPC phenotype. We realize that siRNA treatments transiently relieve REST-mediated transcriptional repression, and that the impact of sustained REST-ablation remains to be determined. However, we hypothesize that epigenetic factors are preventing the expression of core SCNPC transcription factors (NEURO II panel of genes) that would permit SCNPC transdifferentiation in AR-null and AR-expressing cells with REST knockdown. Indeed, the epigenomes of NE and adenocarcinoma tumors are significantly different and EZH2 inhibitors have been shown to reactivate AR expression in some SCNPC models (18, 63). On the other hand, SRRM4-mediated splicing of REST and other neuronal regulators can drive ARPC-SCNPC transition (24). Our results demonstrated that SRRM4-mediated splicing of REST occurs in both AMPC and SCNPC PDX models and in AMPC VCaP cells, suggesting that SRRM4 expression alone is not sufficient to drive SCNPC conversion in all cases. Concordantly, overexpression of SRRM4 converted DU145 cells to a classical SCNPC phenotype but failed to do so in PC-3, 22Rv1, and LNCaP cells (64), implying that multiple hits to the cellular blueprint are required for complete lineage switching. Furthermore, REST directly represses SRRM4 expression and loss of REST activity has been proposed as a feed-forward mechanism for SCNPC conversion (25, 62). Whether loss of REST activity mediates increased SRRM4 expression or increased SRRM4 activity mediates loss of REST requires further examination. Nevertheless, our data clearly show that the homeostatic regulation of the SRRM4-REST axis is required for epithelial differentiation and function.

In summary, our comprehensive analysis of end-stage mCRPC highlights the use of AR and REST transcriptional programs to categorize mCRPC phenotypes in the abiraterone/enzalutamide era. In addition, the data generated in this report could be exploited through biopsy or blood-based biomarkers in future therapeutic studies to define inclusion criteria. This approach could stratify patients according to mCRPC phenotypes and account for the mCRPC disease continuum to implement targeted therapies.

Methods

Tissue acquisition. Biospecimens were obtained within 8 hours of death from patients who died of metastatic CRPC. Visceral metastases were identified at the gross level, bone biopsies were obtained according to a previously described template (65) from 16–20 different sites, and metastases were identified at a histological level. LuCaP PDX lines were established from specimens acquired at either radical prostatectomy or at autopsy, implanted, and maintained by serial passage in immune compromised male mice (66).

Cell lines. All cells were maintained at 37°C in humidified Steri-Cult CO_2 incubators (Thermo Fisher Scientific). C4-2B (gift from L. Chung, Cedars-Sinai Medical Center, Los Angeles, CA), PC-3 (ATCC), and PacMet AR-null cells (5) were maintained in RPMI-1640 Media (Gibco, Life Technologies) with 10% fetal bovine serum (Atlanta Biologicals). VCaP cells (ATCC) were maintained in DMEM (ATCC) with 10% fetal bovine serum (Atlanta Biologicals).

Transient transfections. Cells were suspended in Nucleofector Solution V (Lonza) and 5 μL of 50-μM ON-TARGETplus pooled REST siRNA or control siRNA (Dharmacon). Cell suspensions were electroporated using the Nucleofector II device (Lonza) and program T-027 and then replated in complete media. Forty-eight hours after transfection, cells were harvested for RNA or protein for subsequent analysis.

Immunohistochemistry. The antibodies used in this study are listed in Supplemental Table 1. Five-micron-thick sections of the TMAs were deparaffinized and rehydrated in sequential xylene and graded ethanol. Antigen retrieval was performed in 10 mM citrate buffer (pH 6.0) in a pressure cooker for 30 minutes. Endogenous peroxidase and avidin/biotin were blocked respectively (Vector Laboratories). Sections were then blocked with 5% normal goat-horse-chicken serum, incubated with primary antibody (Supplemental Table 1), incubated with biotinylated secondary antibody (Vector Laboratories), followed by ABC reagent (Vector Laboratories), and stable DAB (Thermo Fisher Scientific). All sections were lightly counterstained with hematoxylin and mounted with Cytoseal XYL (Richard Allan Scientific). Mouse or rabbit IgG was used as negative control. IHC scores were represented as values between 0–200 and were determined as previously described (15).

Immunofluorescence. Formalin-fixed, paraffin-embedded (FFPE) patient and LuCaP PDX tumors were prepared according to the above methods up to and including antigen retrieval. For cells in culture, VCaP cells were seeded on chamber slides (Nunc Lab-Tek; Thermo Fisher Scientific) in complete media 24 hours prior to fixing. Cells were fixed and permeabilized with ice-cold methanol for 10 minutes and then washed in PBS. Cells and sections were blocked for 1 hour with 5% normal goat-horse-chicken serum, incubated for 1 hour (cells) or overnight (sections) with primary antibodies in blocking buffer, washed, and then incubated with fluorescent secondary antibodies for 45 minutes in the dark. All incubations occurred at room temperature and antibodies used are listed in Supplemental Table 1. Slides were mounted using ProLong Gold Antifade Mountant with DAPI (Thermo Fisher Scientific) and then visualized and imaged at ×20 on an Olympus BX41 Fluorescence Microscope.

Immunoblot analysis. Protein extracts from LuCaP PDXs and cell lines were obtained using the Nuclear Extract Kit (Active Motif) according to the manufacturer's protocols. Quantification of total protein was determined using the ProStain Protein Quantification Kit (Active Motif) according to the manufacturer's protocols. Ten to twenty micrograms of total protein lysate was electrophoresed on 4%–15% Bis-Tris gels (Bio-Rad Laboratories) with 1× Tris/Glycine/SDS Buffer (Bio-Rad Laboratories). The proteins were transferred to PVDF that was blocked with 5% Blotting-Grade Blocker (Bio-Rad Laboratories) in TBS/0.1% Tween-20 and subsequently probed with primary and secondary antibodies (Supplemental Table 1). Proteins were visualized using Clarity Western ECL Substrate (Bio-Rad Laboratories).

RNA isolation. Total RNA was isolated from 98 tissue samples of CRPC metastases, which had been frozen in OCT (Tissue-Tek) with RNA STAT-60 (Tel-Test). Using an H&E-stained slide for each sample for orientation, 1-mm core punches of tumor were obtained. Alternatively, multiple sections enriched for tumor were cut using a Leica CM3050S cryostat. Total RNA was isolated from flash-frozen LuCaP PDX tissues or cell lines with RNA STAT-60 (Tel-Test) followed by purification with RNeasy Mini Kit (Qiagen) using the manufacturer's recommended in-solution DNase digestion (Qiagen). The purity and yield of the RNA were determined on a NanoDrop 2000 (Thermo Fisher Scientific). RNA integrity was assessed on a 2100 Bioanalyzer (Agilent Technologies).

PCR and sequencing. First-strand cDNA synthesis was performed with 1 μg RNA using an Advantage RT-for-PCR Kit (Clontech Laboratories). PCR was performed using either Platinum SYBR Green qPCR SuperMix-UDG (Invitrogen; real-time PCR) or HotStarTaq Plus Master Mix (Qiagen; PCR for sequencing) on a Rotor-Gene Q (Qiagen). PCR primers (Integrated DNA Technologies) specific for *REST* were adapted from Raj et al. (25). The REST 5′ primer-GAGAACGCCCATATAAATGTGAAC and 3′ primer-CGGGTTACTTCATGTTGATTAGAG were used. The PCR reaction parameters were as follows: 50°C for 2 minutes and 95°C for 2 minutes (one cycle), followed by 30 cycles (standard gels) or 40 cycles (band sequencing) at 95°C for 10 seconds, annealing/extension at T(m) for 30 seconds, and 72°C for 30 seconds; the final extension was 72°C for 7 minutes. *REST* and *REST4* PCR products were visualized after electrophoresis on a 1.2% agarose gel. For sequencing, PCR product bands were dissected out and purified using the QIAquick Gel Extraction Kit (Qiagen). The purified product was then sequenced by Eurofins Genomics using their Standard Read sequencing chemistry.

RNA sequencing. RNA-Seq libraries were constructed from 1 μg total RNA using the Illumina TruSeq Stranded mRNA LT Sample Prep Kit according to the manufacturer's protocol. Barcoded libraries were pooled and sequenced on the Illumina HiSeq 2500 generating 50 bp paired end reads. Sequencing reads were mapped to the hg38 human using TopHat v2.1.0 (67). For PDX samples, sequences were also aligned to the mm10 mouse genome and those derived from potential contamination with mouse tissue were removed from the analysis as previously described (68). Gene level abundance was quantified from the filtered human alignments in R using the GenomicAlignments Bioconductor package (69). Differential expression was assessed using transcript abundances as inputs to the edgeR Bioconductor package in R (70). For edgeR analysis, genes filtered for a minimum expression level of at least 1 count per million reads (CPM) in at least 2 samples were used to calculate expression differences using an exact test with a negative binomial distribution, applying a significance level of 0.05 with Benjamin-Hochberg false discovery rate (FDR) adjustment. The RNA-Seq data from this report can be accessed through GEO at GSE126078 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE126078).

Pathway analysis. Gene expression results were ranked by their edgeR statistics and used to conduct Gene Set Enrichment Analysis (GSEA) to determine patterns of pathway activity in different treatment groups. We used the curated pathways from within the MSigDBv6.1. Gene ontology (GO) enrichment of Venn diagram groups was computed using GOrilla with default parameters (71). The target and background list option was used and gene sets with enrichment of $P < 0.001$ were considered significant.

Multidimensional scaling (MDS) plots. Specimens were classified according to expression of NEURO I, NEURO II, AR, and SQUAM gene signatures. ARPC and ARLPC phenotypes were differentiated based on AR or KLK3 expression (RNA-Seq) with ALRPC possessing an AR $\log_2$ FPKM value less than 4.0 or a KLK3 $\log_2$ FPKM value less than 2.0. Phenotypic groups were visualized using classical multidimensional scaling (MDS) calculated with the cmdscale function in R using the expression profiles of the 26 genes from the combined lists of NEURO I, NEURO II, AR, and SQUAM gene signatures. The distance metric was euclidean calculated by dist function on the columns (samples). The RNA-Seq data from the Stand Up To Cancer mCRPC cohort were accessed using dbGaP accession phs000915.v2.p2.

Statistics. Sample size for each experiment is indicated in the figure legends. Experiments were repeated a minimum of 2 times. Statistical analyses for RNA sequencing, pathway analyses, and MDS were performed as indicated using R software. The enrichment scores were calculated in R using the GSVA package using the 14 genes in the NEURO I and NEURO II gene sets for NEURO scores and a previously published set of AR-regulated genes for AR-activity scores (5, 72). Mean AR-activity scores in transfected C4-2B cells were graphed using GraphPad Prism software.

Study approval. All rapid autopsy tissues were collected from patients who had signed written informed consent under the aegis of the Prostate Cancer Donor Program at the University of Washington (73). The IRB of the University of Washington approved this study. All patient-derived xenograft experiments were approved by the University of Washington IACUC.

Author contributions

MPL, LGB, PSN, and CM conceived and designed the project. IMC, RC, and AK performed sequencing and bioinformatics analyses. MPL, LGB, LK, BL, YCY, and ACH conducted molecular and cell biology experiments. LDT and RMG provided pathology evaluation. HMN, EC, and CM provided biospecimens and patient-derived xenograft models. CSH, EYY, HHC, EAM, BM, MTS, DWL, and PSN consented patients for the rapid autopsy program and/or provided clinical expertise. MPL, PSN, and CM wrote the manuscript, and all authors reviewed and edited the manuscript.

Acknowledgments

This work was supported by a Department of Defense Idea Development Award: Partnering Principal Investigator (W81XWH-17-1-0414;W81XWH-17-1-0415), W81XWH-15-1-0430, PC170431, the Pacific Northwest Prostate Cancer SPORE (P50CA97186), the Department of Defense Prostate Cancer Biorepository Network (W81XWH-14-2-0183), Department of Defense Prostate Cancer Clinical Trials Consortium W81XWH-15-2-0008, National Cancer Institute (NCI) R01 CA230617, NCI P01 CA163227, the Prostate Cancer Foundation, the AACR NextGen Transformative Cancer Research Grant, the Institute for Prostate Cancer Research, and the Richard M. LUCAS Foundation. We would like to thank the patients who generously donated tissue that made this research possible. We would also like to thank Jennifer Conner, Michiyo Dalos, Daniel Sondheim, and the Comparative Medicine Animal Caregivers for assistance with the LuCaP PDX work. Additionally, we would like to thank Paul Lange, Robert Vessella, Funda Vakar-Lopez, Martine Roudier, Xiaotun Zhang, Belinda Nghiem, Jennifer Noteboom, and the rapid autopsy teams in the Urology and Pathology Departments at the University of Washington.

Address correspondence to: Colm Morrissey, Genitourinary Cancer Research Laboratory, Department of Urology, Box 356510, University of Washington, Seattle, Washington 98195, USA. Phone: 206.543.1461; Email: cmorriss@u.washington.edu. Or to: Peter S. Nelson, Divisions of Human Biology and Clinical Research, Fred Hutchinson Cancer Research Center, Mailstop D4-100, 1100 Eastlake, Seattle, Washington 98109-1024, USA. Phone: 206.667.3377; Email: pnelson@fhcrc.org.

1. Heinlein CA, Chang C. Androgen receptor in prostate cancer. *Endocr Rev*. 2004;25(2):276–308.
2. Scher HI, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med*. 2012;367(13):1187–1197.
3. Ryan CJ, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med*. 2013;368(2):138–148.
4. Kumar A, et al. Substantial interindividual and limited intraindividual genomic diversity among tumors from men with metastatic prostate cancer. *Nat Med*. 2016;22(4):369–378.
5. Bluemn EG, et al. Androgen receptor pathway-independent prostate cancer is sustained through FGF signaling. *Cancer Cell*. 2017;32(4):474–489.
6. Aggarwal R, et al. Clinical and genomic characterization of treatment-emergent small-cell neuroendocrine prostate cancer: a multi-institutional prospective study. *J Clin Oncol*. 2018;36(24):2492–2503.
7. van de Vijver MJ, et al. A gene-expression signature as a predictor of survival in breast cancer. *N Engl J Med*. 2002;347(25):1999–2009.
8. Glinsky GV, Glinskii AB, Stephenson AJ, Hoffman RM, Gerald WL. Gene expression profiling predicts clinical outcome of prostate cancer. *J Clin Invest*. 2004;113(6):913–923.
9. Irshad S, et al. A molecular signature predictive of indolent prostate cancer. *Sci Transl Med*. 2013;5(202):202ra122.
10. Sun X, et al. Correlated metabolomic, genomic, and histologic phenotypes in histologically normal breast tissue. *PLoS ONE*. 2018;13(4):e0193792.
11. Pareja F, Geyer FC, Marchiò C, Burke KA, Weigelt B, Reis-Filho JS. Triple-negative breast cancer: the importance of molecular and histologic subtyping, and recognition of low-grade variants. *NPJ Breast Cancer*. 2016;2:16036.
12. Tan PY, Chang CW, Chng KR, Wansa KD, Sung WK, Cheung E. Integration of regulatory networks by NKX3-1 promotes androgen-dependent prostate cancer survival. *Mol Cell Biol*. 2012;32(2):399–414.
13. Cheng WS, Giandomenico V, Pastan I, Essand M. Characterization of the androgen-regulated prostate-specific T cell receptor gamma-chain alternate reading frame protein (TARP) promoter. *Endocrinology*. 2003;144(8):3433–3440.
14. Rickman DS, et al. SLC45A3-ELK4 is a novel and frequent erythroblast transformation-specific fusion transcript in prostate cancer. *Cancer Res*. 2009;69(7):2734–2738.
15. Zhang X, et al. SRRM4 expression and the loss of REST activity may promote the emergence of the neuroendocrine phenotype in castration-resistant prostate cancer. *Clin Cancer Res*. 2015;21(20):4698–4708.
16. Mu P, et al. SOX2 promotes lineage plasticity and antiandrogen resistance in TP53- and RB1-deficient prostate cancer. *Science*. 2017;355(6320):84–88.
17. Bishop JL, et al. The master neural transcription factor BRN2 is an androgen receptor-suppressed driver of neuroendocrine differentiation in prostate cancer. *Cancer Discov*. 2017;7(1):54–71.
18. Beltran H, et al. Divergent clonal evolution of castration-resistant neuroendocrine prostate cancer. *Nat Med*. 2016;22(3):298–305.
19. Park JW, et al. Reprogramming normal human epithelial tissues to a common, lethal neuroendocrine cancer lineage. *Science*. 2018;362(6410):91–95.
20. Lin D, et al. High fidelity patient-derived xenografts for accelerating prostate cancer discovery and drug development. *Cancer Res*. 2014;74(4):1272–1283.
21. Lee N, et al. Interactomic analysis of REST/NRSF and implications of its functional links with the transcription suppressor TRIM28 during neuronal differentiation. *Sci Rep*. 2016;6:39049.
22. Lee JH, Shimojo M, Chai YG, Hersh LB. Studies on the interaction of REST4 with the cholinergic repressor element-1/neuron restrictive silencer element. *Brain Res Mol Brain Res*. 2000;80(1):88–98.
23. Chen GL, Miller GM. Alternative *REST* splicing underappreciated. *eNeuro*. 2018;5(5):ENEURO.0034-18.2018.
24. Li Y, et al. SRRM4 drives neuroendocrine transdifferentiation of prostate adenocarcinoma under androgen receptor pathway inhibition. *Eur Urol*. 2017;71(1):68–78.
25. Raj B, et al. Cross-regulation between an alternative splicing activator and a transcription repressor controls neurogenesis. *Mol Cell*. 2011;43(5):843–850.
26. Coulson JM, Edgson JL, Woll PJ, Quinn JP. A splice variant of the neuron-restrictive silencer factor repressor is expressed in small cell lung cancer: a potential role in derepression of neuroendocrine genes and a useful clinical marker. *Cancer Res*. 2000;60(7):1840–1844.
27. Tran C, et al. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. *Science*. 2009;324(5928):787–790.
28. Chang YT, et al. REST is a crucial regulator for acquiring EMT-like and stemness phenotypes in hormone-refractory prostate cancer. *Sci Rep*. 2017;7:42795.
29. Troyer DA, et al. Characterization of PacMetUT1, a recently isolated human prostate cancer cell line. *Prostate*. 2008;68(8):883–892.
30. Rickman DS, et al. Prediction of future metastasis and molecular characterization of head and neck squamous-cell carcinoma based on transcriptome and genome analysis by microarrays. *Oncogene*. 2008;27(51):6607–6622.
31. Xiao J, et al. Eight potential biomarkers for distinguishing between lung adenocarcinoma and squamous cell carcinoma. *Oncotarget*. 2017;8(42):71759–71771.
32. Accetta PA, Gardner WA. Squamous metastases from prostatic adenocarcinoma. *Prostate*. 1982;3(5):515–521.
33. Malik RD, Dakwar G, Hardee ME, Sanfilippo NJ, Rosenkrantz AB, Taneja SS. Squamous cell carcinoma of the prostate. *Rev Urol*. 2011;13(1):56–60.

34. Zhang Z, et al. Mixed adenocarcinoma, sarcomatoid carcinoma and adenosquamous carcinoma of the prostate: A case report. *Oncol Lett*. 2014;8(5):2325–2327.
35. Bassler TJ, Orozco R, Bassler IC, Boyle LM, Bormes T. Adenosquamous carcinoma of the prostate: case report with DNA analysis, immunohistochemistry, and literature review. *Urology*. 1999;53(4):832–834.
36. Devaney DM, Dorman A, Leader M. Adenosquamous carcinoma of the prostate: a case report. *Hum Pathol*. 1991;22(10):1046–1050.
37. Chao A, et al. Molecular characterization of adenocarcinoma and squamous carcinoma of the uterine cervix using microarray analysis of gene expression. *Int J Cancer*. 2006;119(1):91–98.
38. Hamada T, et al. MUC4: a novel prognostic factor of oral squamous cell carcinoma. *Int J Cancer*. 2012;130(8):1768–1776.
39. Walts AE, Said JW, Siegel MB, Banks-Schlegel S. Involucrin, a marker of squamous and urothelial differentiation. An immunohistochemical study on its distribution in normal and neoplastic tissues. *J Pathol*. 1985;145(4):329–340.
40. Kvedar JC, Manabe M, Phillips SB, Ross BS, Baden HP. Characterization of sciellin, a precursor to the cornified envelope of human keratinocytes. *Differentiation*. 1992;49(3):195–204.
41. Park GT, Lim SE, Jang SI, Morasso MI. Suprabasin, a novel epidermal differentiation marker and potential cornified envelope precursor. *J Biol Chem*. 2002;277(47):45195–45202.
42. Alam H, Sehgal L, Kundu ST, Dalal SN, Vaidya MM. Novel function of keratins 5 and 14 in proliferation and differentiation of stratified epithelial cells. *Mol Biol Cell*. 2011;22(21):4068–4078.
43. Zhang H, et al. Selective expression of S100A7 in lung squamous cell carcinomas and large cell carcinomas but not in adenocarcinomas and small cell carcinomas. *Thorax*. 2008;63(4):352–359.
44. Mongiat M, Otto J, Oldershaw R, Ferrer F, Sato JD, Iozzo RV. Fibroblast growth factor-binding protein is a novel partner for perlecan protein core. *J Biol Chem*. 2001;276(13):10263–10271.
45. Cuzick J, et al. Prognostic value of an RNA expression signature derived from cell cycle proliferation genes in patients with prostate cancer: a retrospective study. *Lancet Oncol*. 2011;12(3):245–255.
46. Sparano JA, et al. Prospective validation of a 21-gene expression assay in breast cancer. *N Engl J Med*. 2015;373(21):2005–2014.
47. Abida W, et al. Genomic correlates of clinical outcome in advanced prostate cancer. *Proc Natl Acad Sci USA*. 2019;116(23):11428–11436.
48. Aparicio AM, et al. Platinum-based chemotherapy for variant castrate-resistant prostate cancer. *Clin Cancer Res*. 2013;19(13):3621–3630.
49. Aparicio AM, et al. Combined tumor suppressor defects characterize clinically defined aggressive variant prostate cancers. *Clin Cancer Res*. 2016;22(6):1520–1530.
50. Epstein JI, et al. Proposed morphologic classification of prostate cancer with neuroendocrine differentiation. *Am J Surg Pathol*. 2014;38(6):756–767.
51. Tsai HK, Lehrer J, Alshalalfa M, Erho N, Davicioni E, Lotan TL. Gene expression signatures of neuroendocrine prostate cancer and primary small cell prostatic carcinoma. *BMC Cancer*. 2017;17(1):759.
52. Shen R, Dorai T, Szaboles M, Katz AE, Olsson CA, Buttyan R. Transdifferentiation of cultured human prostate cancer cells to a neuroendocrine cell phenotype in a hormone-depleted medium. *Urol Oncol*. 1997;3(2):67–75.
53. Deeble PD, Murphy DJ, Parsons SJ, Cox ME. Interleukin-6- and cyclic AMP-mediated signaling potentiates neuroendocrine differentiation of LNCaP prostate tumor cells. *Mol Cell Biol*. 2001;21(24):8471–8482.
54. Labrecque MP, et al. The retinoblastoma protein regulates hypoxia-inducible genetic programs, tumor cell invasiveness and neuroendocrine differentiation in prostate cancer cells. *Oncotarget*. 2016;7(17):24284–24302.
55. Zou M, et al. Transdifferentiation as a mechanism of treatment resistance in a mouse model of castration-resistant prostate cancer. *Cancer Discov*. 2017;7(7):736–749.
56. Ku SY, et al. Rb1 and Trp53 cooperate to suppress prostate cancer lineage plasticity, metastasis, and antiandrogen resistance. *Science*. 2017;355(6320):78–83.
57. Han X, et al. Transdifferentiation of lung adenocarcinoma in mice with Lkb1 deficiency to squamous cell carcinoma. *Nat Commun*. 2014;5:3261.
58. Lee JK, et al. Systemic surfaceome profiling identifies target antigens for immune-based therapy in subtypes of advanced prostate cancer. *Proc Natl Acad Sci USA*. 2018;115(19):E4473–E4482.
59. Inoue K, et al. Interleukin 8 expression regulates tumorigenicity and metastases in androgen-independent prostate cancer. *Clin Cancer Res*. 2000;6(5):2104–2119.
60. van der Deen M, et al. The cancer-related Runx2 protein enhances cell growth and responses to androgen and TGFbeta in prostate cancer cells. *J Cell Biochem*. 2010;109(4):828–837.
61. Lapuk AV, et al. From sequence to molecular pathology, and a mechanism driving the neuroendocrine phenotype in prostate cancer. *J Pathol*. 2012;227(3):286–297.
62. Flores-Morales A, et al. Proteogenomic characterization of patient-derived xenografts highlights the role of REST in neuroendocrine differentiation of castration-resistant prostate cancer. *Clin Cancer Res*. 2019;25(2):595–608.
63. Kleb B, et al. Differentially methylated genes and androgen receptor re-expression in small cell prostate carcinomas. *Epigenetics*. 2016;11(3):184–193.
64. Lee AR, Gan Y, Tang Y, Dong X. A novel mechanism of SRRM4 in promoting neuroendocrine prostate cancer development via a pluripotency gene network. *EBioMedicine*. 2018;35:167–177.
65. Roudier MP, et al. Phenotypic heterogeneity of end-stage prostate carcinoma metastatic to bone. *Hum Pathol*. 2003;34(7):646–653.
66. Nguyen HM, et al. LuCaP prostate cancer patient-derived xenografts reflect the molecular heterogeneity of advanced disease and serve as models for evaluating cancer therapeutics. *Prostate*. 2017;77(6):654–671.
67. Kim D, Pertea G, Trapnell C, Pimentel H, Kelley R, Salzberg SL. TopHat2: accurate alignment of transcriptomes in the presence of insertions, deletions and gene fusions. *Genome Biol*. 2013;14(4):R36.
68. Chou J, et al. Phenotypic and transcriptional fidelity of patient-derived colon cancer xenografts in immune-deficient mice. *PLoS ONE*. 2013;8(11):e79874.
69. Lawrence M, et al. Software for computing and annotating genomic ranges. *PLoS Comput Biol*. 2013;9(8):e1003118.
70. Robinson MD, McCarthy DJ, Smyth GK. edgeR: a Bioconductor package for differential expression analysis of digital gene expression data. *Bioinformatics*. 2010;26(1):139–140.
71. Eden E, Navon R, Steinfeld I, Lipson D, Yakhini Z. GOrilla: a tool for discovery and visualization of enriched GO terms in ranked gene lists. *BMC Bioinformatics*. 2009;10:48.
72. Hänzelmann S, Castelo R, Guinney J. GSVA: gene set variation analysis for microarray and RNA-seq data. *BMC Bioinformatics*. 2013;14:7.
73. Morrissey C, et al. Effects of androgen deprivation therapy and bisphosphonate treatment on bone in patients with metastatic castration-resistant prostate cancer: results from the University of Washington Rapid Autopsy Series. *J Bone Miner Res*. 2013;28(2):333–340.

Germline Genetic Testing in Advanced Prostate Cancer; Practices and Barriers: Survey Results from the Germline Genetics Working Group of the Prostate Cancer Clinical Trials Consortium

Channing J. Paller,[1] Emmanuel S. Antonarakis,[1] Tomasz M. Beer,[2] Hala T. Borno,[3] Maria I. Carlo,[4] Daniel J. George,[5] Julie N. Graff,[6] Shilpa Gupta,[7] Elisabeth I. Heath,[8] Celestia S. Higano,[9] Rana R. McKay,[10] Alicia K. Morgans,[11] Akash Patnaik,[12] Daniel P. Petrylak,[13] Matthew B. Rettig,[14] Charles J. Ryan,[7] Mary-Ellen Taplin,[15] Young E. Whang,[16] Jacob Vinson,[17] Heather H. Cheng,[9] Veda N. Giri,[18] on behalf of the PCCTC Germline Genetics Working Group

Abstract

More than 10% of patients with advanced prostate cancer carry inherited genetic mutations that might amplify their response to targeted therapies, but barriers, including a shortage of genetic counselors, limit patient access to testing that would enable targeted therapy. This study of practices in nineteen US comprehensive cancer centers showed that a shortage of genetic counselors and 4 other barriers limit adoption of this important advance. Herein we also catalogue germline genetic testing practices and illuminate initiatives that might expand testing availability.

Background: Germline genetic testing increasingly identifies advanced prostate cancer (PCa) patients who are candidates for precision therapies. The Prostate Cancer Clinical Trials Consortium (PCCTC) established the Germline Genetics Working Group to provide guidance and resources to expand effective use of germline genetic testing. **Materials and Methods:** A 14-item questionnaire was e-mailed to academic oncologists at 43 PCCTC sites to collect information on germline genetic testing patterns, including patients considered, choice of assays, barriers slowing adoption, and actions to overcome barriers. **Results:** Twenty-six genitourinary oncologists from 19 institutions responded. Less than 40% (10 of 26) reported referring patients to a genetics department, whereas the remainder take personal responsibility for genetic testing and counseling; 16 (62%) consider testing all metastatic PCa patients,

[1]Sidney Kimmel Comprehensive Cancer Center, Department of Urology, Johns Hopkins University, Baltimore, MD
[2]Division of Hematology/Medical Oncology School of Medicine, Oregon Health and Science University Knight Cancer Institute, Portland, OR
[3]Department of Medicine, University of California San Francisco/Helen Diller Family Cancer, San Francisco, CA
[4]Sidney Kimmel Center for Prostate and Urologic Cancers, Memorial Sloan Kettering Cancer Center, New York, NY
[5]Division of Medical Oncology, Department of Medicine and Duke Cancer Institute, Duke University Medical Center, Durham, NC
[6]Division of Hematology and Medical Oncology, VA Portland Health Care System/ Oregon Health & Science University Knight Cancer Institute, Portland, OR
[7]Division of Hematology, Oncology, and Transplantation, University of Minnesota Masonic Cancer Center, Minneapolis, MN
[8]Karmanos Cancer Institute and Department of Oncology, Wayne State University, Detroit, MI
[9]Fred Hutchinson Cancer Research Center and Division of Medical Oncology, Department of Medicine, University of Washington School of Medicine, Seattle, WA
[10]Department of Medicine, University of California at San Diego Moores Cancer Center, La Jolla, CA
[11]Division of Hematology/Oncology, Department of Medicine, Feinberg School of Medicine at Northwestern University, Chicago, IL
[12]Department of Medicine, University of Chicago Comprehensive Cancer Center, Chicago, IL
[13]Department of Urology, Yale Cancer Center, New Haven, CT
[14]Department of Medicine, Division of Hematology-Oncology, David Geffen School of Medicine at UCLA, Los Angeles, CA
[15]Department of Medical Oncology, Dana Farber Cancer Institute, Boston, MA
[16]Department of Medicine, Hematology/Oncology, University of North Carolina Lineberger Cancer Center, Chapel Hill, NC
[17]Prostate Cancer Clinical Trials Consortium, Memorial Sloan Kettering Cancer Center, New York, NY
[18]Department of Medical Oncology, Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA

Submitted: Mar 5, 2019; Accepted: Apr 11, 2019; Epub: Apr 18, 2019

Addresses for correspondence: Heather H. Cheng, MD, PhD, Seattle Cancer Care Alliance, 825 Eastlake Ave E, G4-820, Seattle, WA 98109-1023. Fax: 206-606-2042; or Veda N. Giri, MD, Sidney Kimmel Cancer Center, Thomas Jefferson University, 1025 Walnut St, Suite 1015, Philadelphia, PA 19107
E-mail contact: hhcheng@uw.edu; Veda.Giri@jefferson.edu

1558-7673/$ - see frontmatter
https://doi.org/10.1016/j.clgc.2019.04.013

whereas 3 (12%) consider testing all patients with high-risk local disease; and 7 (27%) use multigene comprehensive pan-cancer panels, and 14 (54%) use smaller or targeted cancer gene panels. Barriers to widespread use are: (1) delayed or limited access to genetic counseling; (2) no insurance coverage; (3) lack of effective workflows; (4) insufficient educational materials; and (5) time and space constraints in busy clinics. The primary limitation was the <50% (19 of 43) response from PCCTC sites and no coverage of nonacademic cancer treatment facilities. **Conclusion:** Joint efforts by urologists, oncologists, genetics counselors, insurers, and cancer centers can accelerate implementation of integrated germline genetic services for personalized treatment and clinical trial eligibility for PCa patients.

Clinical Genitourinary Cancer, Vol. 17, No. 4, 275-82
Keywords: BRCA, DNA repair, Lynch, PARP inhibitors, Pembrolizumab

Introduction

A significant number of prostate cancer (PCa) cases have a heritable component. Germline DNA damage repair (DDR) defects are present in >10% of patients who develop metastatic PCa (mPCa), with defects in breast cancer *(BRCA2)* found in more than 5% and defects in *BRCA1*, ataxia-telangiectasia mutated *(ATM)*, and checkpoint kinase 2 genes each found in 1% to 2%. Prevalence of germline mutations in DDR genes in men with mPCa exceeded the observed 5% prevalence in men with localized PCa and 3% prevalence in men without a known cancer diagnosis.[1,2] In recent years, the treatment landscape for mPCa has been refined by the discovery of DDR deficiency as predictive biomarkers for response to targeted therapies. For example, the presence of homologous recombination deficiency might predict response to poly (adenosine diphosphate-ribose) polymerase inhibitors as well as to other DNA-damaging chemotherapy agents (platinum chemotherapy).[3-6] Similarly, the presence of germline mutations in mismatch repair (MMR) genes might identify candidates for treatment with immune checkpoint inhibitors.[7-10] Thus, it has become progressively important to assess practice patterns and needs regarding germline genetic testing and counseling for men with PCa. Urologists are increasingly ordering germline testing for their PCa patients in light of recent evidence that *BRCA1/2* and *ATM* mutation status is associated with grade reclassification or PCa patients undergoing active surveillance.[11] Urology involvement in germline genetic testing will grow as the area evolves to include high-risk localized (HRL) and earlier disease states.[12-14]

The Germline Genetics Working Group (GGWG) of the Prostate Cancer Clinical Trials Consortium (PCCTC) was established in June 2017 in response to the need to better inform and advise clinicians of the increasing evidence that germline alterations in DDR genes might identify additional options for PCa therapy. The objectives of the GGWG are to work together with clinicians and researchers around topical challenges of treatment selection and eligibility for trials of investigational therapeutics, and to enable more streamlined and effective use of germline genetic testing in PCa patients in the face of a rapidly evolving genetics-informed therapeutic landscape.

In June 2018, the GGWG produced a white paper that presented a framework to address unique challenges and therapeutic opportunities regarding germline testing for precision therapy in patients with advanced PCa and identified areas of future research.[15] In the white paper the GGWG recommended that clinicians: (1) consider expanding germline genetic testing beyond cancer risk assessment to inform treatment selection and eligibility for clinical trials; (2) work with genetic counselors to ensure pretest informed decision-making through education or counseling and post-testing counseling; and (3) where appropriate, ensure mechanisms for offering cascade germline genetic testing to family members. However, barriers and challenges to broader implementation of these recommendations require attention.

To elucidate practice patterns and challenges in germline genetic testing of PCa patients in oncology, the GGWG surveyed medical oncologists from institutions who were members of the PCCTC. Herein, we report survey data from responding oncologists from 19 PCCTC cancer centers identifying commonalities and differences in practice patterns. The survey results were used to support recommendations for addressing barriers to germline testing for men with PCa and are placed in the context of current National Comprehensive Cancer Network (NCCN) guidelines for genetic testing of PCa patients.

Materials and Methods

Survey

A 14-question survey was developed by the GGWG to capture data on the practice patterns and needs of oncologists at PCCTC institutions. The survey was refined after pilot testing and then distributed to oncologists at their institutions using RedCap, a Web-based survey tool, with an e-mail (December 20, 2017) asking members to complete the survey and to ask other investigators at their institutions to respond. A reminder e-mail was sent on January 16, 2018 to GGWG members who had not completed the survey. PCCTC principal investigators were reminded of the survey during 2 sequential monthly conference calls that took place between the 2 e-mail survey distributions (December 21, 2017 and January 8, 2018).

The survey questions offered multiple choice answer selections on personal practices around genetics services, on patient characteristics oncologists consider for germline testing (metastatic disease, advanced stage, family history), on cascade genetic testing processes, and on gene panels. The remainder were free-form questions asking for clarifications of answers to the multiple-choice questions and also asking participants to describe their approaches to integrating

Table 1 Cancer Centers Providing Germline Genetic Testing Survey Responses

Cancer Center	Responses
Fred Hutchinson Cancer Research Institute	3
Johns Hopkins Sidney Kimmel Comprehensive Cancer Center	3
Lurie Comprehensive Cancer Center	2
Rush University Medical Center	2
Weill Cornell Medical College	2
Beth Israel Deaconess Cancer Center	1
Carbone Cancer Center	1
Dana-Farber Cancer Institute	1
Duke Comprehensive Cancer Center	1
Jonsson Comprehensive Cancer Center	1
Lineberger Comprehensive Cancer Center	1
Masonic Cancer Center	1
Memorial Sloan Kettering Cancer Center	1
Moores Cancer Center	1
Oregon Health and Science University Knight Cancer Institute	1
Sidney Kimmel Cancer Center at Thomas Jefferson University	1
University of Chicago Medicine Comprehensive Cancer Center	1
Wayne State Karmanos Cancer Institute	1
Yale Cancer Center	1

germline testing with therapeutic clinical trials and to cascade testing. The full survey is shown in Supplemental Appendix 1 in the online version).

Analysis

Data were gathered in the RedCap package and exported to a comma-separated value file. Data were imported into Excel (Version 16.18, Microsoft Corp, Redmond, WA), where they were summarized, tabulated, and graphed.

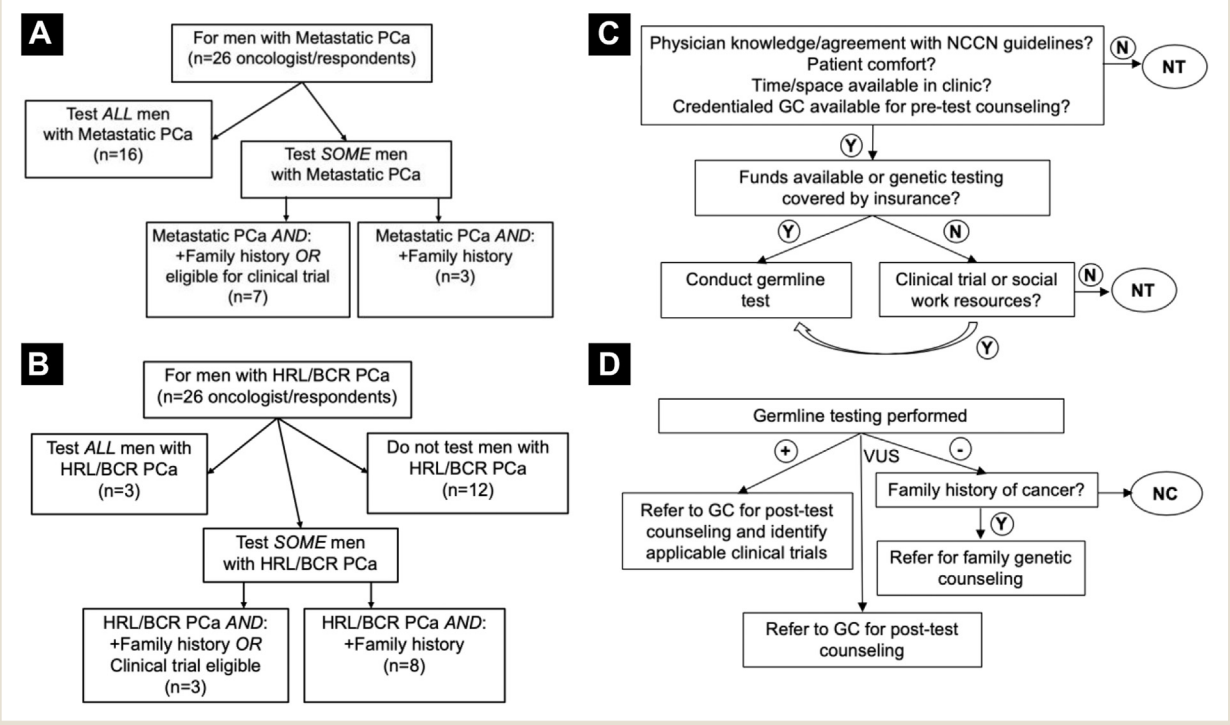
Results

Between December 20, 2017 and April 3, 2018, representatives of the 43 PCCTC participating and affiliate sites received the germline genetic testing current practice survey and an e-mail encouraging redistribution to institutional colleagues, and 26 PCa oncologists from 19 sites (44%) completed the survey (Table 1).

Personal Practices of PCa Oncologists Regarding Genetics Services for PCa Patients

Whereas 10 of 26 (38%) participating oncologists reported that they refer patients to a separate department for genetic testing and counseling, more than half reported taking personal responsibility for some or all genetic education and testing of their patients. Four (15%) reported personally performing pretest counseling, ordering germline testing, and performing post-test counseling. Those who reported using a combination of approaches generally referred to

Figure 1 Provider Considerations of Germline Testing Among Men With Prostate Cancer. (A) Men With Metastatic Prostate Cancer (PCa) Considered for Germline Testing. (B) Men With High-Risk Localized (HRL) and Biochemically Recurrent (BCR) PCa Considered for Germline Testing. (C) Factors Affecting Decision to Test. (D) Factors Affecting Decisions on Results



Abbreviations: + = positive results; GC = genetic counselor; N = no; NC = no post-test genetic counseling; NCCN = National Comprehensive Cancer Network; NT = no germline genetic testing; VUS = variant of uncertain significance; Y = yes.

Table 2 Approaches to Germline Cancer Predisposition Testing

General Approach to Germline Cancer Predisposition Testing[a]	Respondent																									
	11	6	10	17	21	1	22	18	20	16	19	13	2	8	12	3	15	7	24	5	25	26	23	4	9
Comprehensive, Pan-Cancer Panel	•	•	•	•	•	•	•	•																	
Expanded Cancer Panel (eg, Lynch and *BRCA1/2* and Hereditary Breast and Ovarian Cancer Genes)	•								•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
Limited Prostate Cancer-Specific Panel																							•		
Specific Individual Genes (eg, *BRCA1, BRCA2*)																								•	•
Clinical Trial-Focused Panel	•																								

[a]Sites that listed multiple approaches (eg, comprehensive and limited) explained that lack of insurance or limited patient capacity to pay sometimes causes them to select a more limited panel.

genetic counselors for post-test counseling. Variation in practice appears to depend on factors such as: (1) patient's insurance coverage for genetic testing and counseling; (2) availability of testing and counseling resources within the oncology group; (3) testing and counseling resources in a separate genetics department; and (4) wait times for referrals.

Patients Considered for Germline Genetic Testing

Metastatic PCa. All 26 participating oncologists reported considering some mPCa patients for germline genetic testing: 16 (62%) reported considering all mPCa patients; 7 (27%) considered testing mPCa patients with a family history and/or who were eligible for clinical trials; and 3 (12%) considered testing only for patients with a family history for germline genetic testing (Figure 1A).

High-Risk Localized PCa Patients and Non-mPCa. More than half of the participating oncologists, 14 of 26 (54%), considered germline genetic testing for some PCa patients with HRL or non-mPCa (nmPCa), whereas 12 (46%) did not consider germline testing for these patients. Three (12%) reported testing all HRL/nmPCa patients; 3 (12%) reported considering testing only for patients with a family history for germline genetic testing; and 8 (31%) reported considering testing only those with a family history of cancer (Figure 1B).

Operational Barriers Faced by Oncologists Considering Germline Genetic Testing for PCa Patients

On the basis of participant responses and free text comments, 5 barriers in streamlining genetic testing were identified: access to genetic counselors, insurance coverage and cost, clinic workflow, time and space availability, and access to resources for provider and patient education. Figure 1C shows the role of those operational barriers and the flow of considerations on whether to conduct germline genetic testing reported by responding oncologists, whereas Figure 1D shows how referral decisions are made on the basis of those results.

Reported Germline Testing Approaches

Participating oncologists reported their approaches for germline cancer predisposition testing. Seven of 26 (27%) reported using only "comprehensive pan-cancer panels," whereas 14 (54%) listed only "expanded cancer panels (eg, Lynch and *BRCA1/2* and hereditary breast and ovarian cancer genes)," and 4 others (15%) reported using more than 1 type of panel. One participant did not answer this question (Table 2).

Resources for Patients and Family Members Regarding Genetic Testing

The GGWG aggregated a list of Web sites that it has found valuable for educating patients and their families about germline genetic testing for PCa (Table 3). Two participants reported they are developing local resources (a video and an information sheet for patients).

Discussion

The relevance of germline genetic testing in PCa is emerging today as it did in breast cancer 3 decades ago, although in PCa it is

Table 3 Web Resources for Educating PCa Patients and Families About Germline Genetic Testing

Source	URL	Content
Color	https://www.color.com/learn/can-cancer-be-inherited	Patient-friendly discussion and data about cancer due to inherited (germline) genetic mutations
Dana Farber	https://www.dana-farber.org/cancer-genetics-and-prevention/videos/	Videos explaining topics in cancer genetics and testing
Invitae	https://www.invitae.com/en/patients/genetic-diagnosis/	Brief descriptions of genetic testing
Memorial Sloan Kettering	https://www.mskcc.org/cancer-care/risk-assessment-screening/hereditary-genetics/genetic-counseling/inherited-risk-prostate	Very brief discussion of inherited risk of PCa
National Society of Genetic Counselors	https://www.nsgc.org/	Comprehensive guidance for patients, including help finding counselors
Prostate Cancer Foundation	https://www.pcf.org/news/genetic-screening-guidelines-for-prostate-cancer/	High-level overview of genetics-related knowledge helpful to patients with PCa and their families
	https://www.pcf.org/patient-resources/family-cancer-risk/genetic-testing-prostate-cancer/	Recommendation to speak with physician about whether patients need genetic testing, with 5 more detailed subpages
Sidney Kimmel Cancer Center of Thomas Jefferson University	https://prostategenetics.jeffersonhealth.org/	PCa-focused and patient-friendly, Web-based resource explaining genetic counseling, genetic testing, family history, genes, and cancer risks

Abbreviation: PCa = prostate cancer.

accompanied by concurrent therapeutic relevance. These rapid and exciting changes have resulted in challenges illustrated by the 2018 PCCTC GGWG survey of medical PCa oncologists at academic institutions in the PCCTC consortium, around their practices in germline genetic testing of PCa patients. The survey identified common themes across 19 institutions as well as substantial

Table 4 Therapeutic and Delivery Model Clinical Trials in PCa With Relevance for Germline Genetic Eligibility Criteria

Phase	Title	Disease State	Abbreviated Title	Clinicaltrials.gov
Therapeutic Trials				
III	Study of Olaparib (Lynparza™) Versus Enzalutamide or Abiraterone Acetate in Men With Metastatic Castration-Resistant Prostate Cancer (PROfound Study)	mCRPC	PROFOUND	NCT02987543
III	A Study of Rucaparib Versus Physician's Choice of Therapy in Patients With Metastatic Castration-resistant Prostate Cancer and Homologous Recombination Gene Deficiency	mCRPC	TRITON3	NCT02975934
II	An Efficacy and Safety Study of Niraparib in Men With Metastatic Castration-Resistant Prostate Cancer and DNA-Repair Anomalies	mCRPC	GALAHAD	NCT02854436
II	A Study of Rucaparib in Patients With Metastatic Castration-resistant Prostate Cancer and Homologous Recombination Gene Deficiency	mCRPC	TRITON2	NCT02952534
II	A Study of Talazoparib in Men With DNA Repair Defects and Metastatic Castration-Resistant Prostate Cancer	mCRPC		NCT03148795
II	Olaparib in Men With High-Risk Biochemically-Recurrent Prostate Cancer Following Radical Prostatectomy, With Integrated Biomarker Analysis	BCR		NCT03047135
II	Abiraterone/Prednisone, Olaparib, or Abiraterone/Prednisone + Olaparib in Patients With Metastatic Castration-Resistant Prostate Cancer With DNA Repair Defects	mCRPC	BRCAaway	NCT03012321
Pilot	Docetaxel and Carboplatin in Treating Patients With Metastatic, Castration Resistant Prostate Cancer Containing Inactivated Genes in the BRCA 1/2 Pathway	mCRPC	ABCD	NCT02598895
II	Docetaxel and Carboplatin for Patients With mCRPC and DNA-Repair Deficiencies	mCRPC	V-ABCD	NCT02985021
II	Trial of Rucaparib in Patients With Metastatic Hormone-Sensitive Prostate Cancer Harboring Germline DNA Repair Gene Mutations	mHSPC	TRIUMPH	NCT03413995
Delivery Model Trials				
NA	Evaluating an Alternative Clinical Genetics Cancer Care Delivery Model: A Pilot Study of Patient Outcomes	PCa		NCT02917798
NA	Genetic Evaluation of Men (GEM)	PCa	GEM Registry	NCT03076242
NA	Genetic Counseling Processes and Outcomes Among Males With Prostate Cancer (ProGen)	PCa	ProGen	NCT03328091
NA	Genetic Testing for Men With Metastatic Prostate Cancer	mPCa	GENTleMEN	NCT03503097

Abbreviations: BCR = biochemical recurrence; mCRPC = metastatic castration-resistant prostate cancer; mHSPC = metastatic hormone-sensitive prostate cancer; mPCa = metastatic prostate cancer; PCa = prostate cancer.

variation in those practices. Five barriers to obtaining genetic testing were identified: lack of timely access to genetic counselors, lack of insurance coverage or high patient out-of-pocket costs, lack of integrated clinic workflow, time and space constraints, and insufficient resources for provider and patient education. Our survey showed that more than half of oncologists reported taking part or full responsibility for germline genetic testing and education/counseling, despite the fact that most oncologists are not trained in genetic counseling.[16] Nearly 40% (10 of 26) of the participating oncologists reported that among mPCa patients, they considered germline genetic testing mainly for patients with a family history of cancer and those who were eligible for a clinical trial with genetic eligibility criteria, rather than all mPCa patients. Germline testing results are increasingly important for consideration of clinical trial eligibility. PCCTC sites reported 10 therapeutic trials for PCa patients with relevance to germline mutations and 4 trials testing new models of genetics delivery in PCa (Table 4). Similarly, a little more than half of respondents reported considering germline genetic testing for patients with HRL PCa and nmPCa. These responses might reflect a period of limited resources and substantial logistical barriers and the need for triaging and prioritization of genetic counseling and testing until barriers can be better addressed.

At the time the survey was distributed, the NCCN guidelines did not include recommendations for germline testing for most PCa patients. On the basis of recent data of germline mutations in men with PCa, before all GGWG survey responses were returned, NCCN prostate guidelines (version 4.2018) were expanded to recommend consideration of germline genetic testing for most metastatic and HRL PCa patients.[17] Thus, the survey captured change in action.

The current guidelines recommend consideration of germline testing for all patients with high-risk and very high-risk local disease, regional disease, and metastatic disease. Further, with more sensitive techniques for early identification of metastatic disease such as prostate specific membrane antigen, fluciclovine,[18] and choline,[19,20] more patients might be classified as metastatic than in the past, further increasing the numbers of patients to be considered for germline genetic testing. This expansion of patient populations to be considered for genetic testing, together with the barriers reflected in our findings, highlight the need for dedicated education and training for radiation oncologists, urologists, and medical oncologists. In the localized disease setting with risk levels that are very low, low, favorable intermediate, and unfavorable intermediate, the NCCN prostate guidelines suggest consideration for germline testing on the basis of a strong family history of PCa and/or other primary cancers, or for patients with a relative with a known familial cancer risk syndrome.

The current NCCN prostate guidelines also suggest that patients whose tumor testing is positive for microsatellite instability-high or deficient-MMR (indicating potential use of pembrolizumab in treatment for metastatic castration-resistant PCa (mCRPC), also be referred for genetic counseling to assess for the possibility of Lynch syndrome. Finally, the current NCCN guidelines recommend that physicians consider testing tumors of patients with mCRPC for germline and somatic mutations in *BRCA1*, *BRCA2*, *ATM*, partner and localizer of *BRCA2* and Fanconi anemia complementation group A genes.

Approximately half of survey participants indicated that they would refer patients for genetic counseling and dedicated confirmatory germline testing if a tumor mutation was potentially germline in nature (thus with family counseling implications[21]) consistent with the recommendation in the GGWG white paper.[15] As tumor sequencing for targeted treatment opportunities increase in PCa, the likelihood of identifying mutations that are potentially germline might increase, raising the need for distinct workflows to address this specific clinical scenario.

Several respondents noted that patient willingness to undergo germline genetic testing could be affected by concerns about genetic discrimination for life, disability, and long-term care insurance. The Genetic Information Nondiscrimination Act (GINA) of 2008[22] provides protection from genetic discrimination in health insurance and employment in most employment scenarios, but does not cover life insurance, long-term care, disability insurance, Indian Health Service, federal employees enrolled in the Federal Employee Health Benefits Plan, and other specific Veterans Administration or US military plans. Because of these gaps in protection by the GINA law and potential changes over time, patients approached about germline testing need to consider these issues and their own financial situations before proceeding with germline testing. Thus, providers and patients can benefit from educational and practice-ready resources to help address the need to discuss genetic discrimination laws.

There are some limitations to consider in our results. Urologists were not surveyed, because metastatic disease has been a key driver of genetic testing up to the present time. However, because guidelines for testing are expanding to earlier-stage disease, including urologists in future surveys will add important information. Our analysis does not account for institutional limitations that might have informed physician decisions regarding whom to test. In addition, there were site-specific differences in clinical trial availability with germline genetic eligibility criteria, including in the nmPCa setting which would have influenced consideration of genetic testing for that group. Another limitation is the response rate (oncologists from only 19 of 43 PCCTC sites responded), and the composition of respondents being largely oncologists with specific focus on PCa in academic centers. Nevertheless, we believe that the general concepts around the clinical need for better integration of germline genetic testing in PCa care and the current barriers to implementation will be broadly applicable across oncology practice settings.

Conclusion

The NCCN and other professional organizations advocate informed decision-making for patients in the pretest setting.[23-27] Research to improve delivery of pretest education and optimization of informed decision-making is key to streamlining genetic testing for men with PCa. In the post-test setting, discussion with a genetic counselor is important for patients with germline mutations,

variants of uncertain significance, and with no mutations but with a family history of cancer to ensure understanding of results and appropriate follow-up with regard to additional cancer screening and cascade testing recommendations. Physicians ordering genetic testing need to be well versed in cancer risk guidelines for screening, genetic results interpretation, GINA laws, and population-level cancer screening guidelines. Although referral to a genetic counselor is preferred when possible, there is a recognized shortage of genetic counselors that is predicted to worsen,[28,29] suggesting a role for subspecialty oncologists with training in genetics as well as for genetics training for oncology providers who perform aspects of genetic counseling themselves.[30] Registries that include germline data, family history, treatments, and outcomes such as those being developed in the GEM (Genetic Evaluation of Men), GENTLeMEN (Genetic Testing for Men With Metastatic Prostate Cancer), and ProGen (Genetic Counseling Processes and Outcomes Among Males With Prostate Cancer) trials, along with systems to address barriers to genetic testing, will help inform future guidelines and facilitate integrated genetic testing and counseling services into busy clinical practices.

Clinical Practice Points

- In the context of an evolving therapeutic landscape for men with mPCa and expanding NCCN guidelines for germline testing for patients with earlier stage disease, oncologists and urologists will increasingly need to consider incorporating genetic education, counseling, and germline testing for men with PCa.
- Providing guideline-concordant care now requires that practices and institutions prioritize including germline genetic testing as part of optimal care delivery.
- Physicians, advanced practice providers, genetic counselors, practice managers, and other team members must work in a concerted manner to overcome these barriers in practice- and resource-specific ways for this evolving care model.

Acknowledgments

The authors gratefully acknowledge support from the Prostate Cancer Foundation, the Institute for Prostate Cancer Research, the Pacific Northwest Prostate Cancer National Institutes of Health Specialized Programs of Research Excellence (SPORE) CA097186, National Cancer Institute (NCI) Center Core Grants (P30 CA008748 and P30 CA006973), NCI K23 CA197526, and UL1 TR002319. This work was supported by the Office of the Assistant Secretary of Defense for Health Affairs, through the Prostate Cancer Research Program under award numbers W81XWH-17-2-0043, W81XWH-17-2-0018, W81XWH-17-2-0017, W81XWH-17-2-0020, W81XWH-17-2-002, W81XWH-17-2-00221, W81XWH-17-2-0027, and W81XWH-15-2-0018. Opinions, interpretations, conclusions, and recommendations are those of the authors and are not necessarily endorsed by the Department of Defense.

Disclosure

The authors have stated that they have no conflicts of interest.

Supplemental Data

The supplemental appendix accompanying this article can be found in the online version at https://doi.org/10.1016/j.clgc.2019.04.013.

References

1. Giri VN, Obeid E, Gross L, et al. Inherited mutations in men undergoing multigene panel testing for prostate cancer: emerging implications for personalized prostate cancer genetic evaluation. *JCO Precis Oncol* 2017; 1:1-17.
2. Pritchard CC, Mateo J, Walsh MF, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. *N Engl J Med* 2016; 375:443-53.
3. Mateo J, Carreira S, Sandhu S, et al. DNA-repair defects and olaparib in metastatic prostate cancer. *N Engl J Med* 2015; 373:1697-708.
4. Cheng HH, Pritchard CC, Boyd T, Nelson PS, Montgomery B. Biallelic inactivation of BRCA2 in platinum-sensitive metastatic castration-resistant prostate cancer. *Eur Urol* 2016; 69:992-5.
5. Pennington KP, Walsh T, Harrell MI, et al. Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube, and peritoneal carcinomas. *Clin Cancer Res* 2014; 20:764-75.
6. Scott CL, Swisher EM, Kaufmann SH. Poly (ADP-ribose) polymerase inhibitors: recent advances and future development. *J Clin Oncol* 2015; 33:1397-406.
7. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science* 2017; 357:409-13.
8. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med* 2015; 372:2509-20.
9. Boudadi K, Suzman DL, Anagnostou V, et al. Ipilimumab plus nivolumab and DNA-repair defects in AR-V7-expressing metastatic prostate cancer. *Oncotarget* 2018; 9:28561-71.
10. De Bono JS, Goh JCH, Ojamaa K, et al. KEYNOTE-199: pembrolizumab (pembro) for docetaxel-refractory metastatic castration-resistant prostate cancer (mCRPC). *J Clin Oncol* 2018; 36(15 suppl):5007.
11. Carter HB, Helfand B, Mamawala M, et al. Germline mutations in ATM and BRCA1/2 are associated with grade reclassification in men on active surveillance for prostate cancer. *Eur Urol* 2019; 75:743-9.
12. Giri VN, Hegarty SE, Hyatt C, et al. Germline genetic testing for inherited prostate cancer in practice: implications for genetic testing, precision therapy, and cascade testing. *Prostate* 2019; 79:333-9.
13. Nicolosi P, Ledet E, Yang S, et al. Prevalence of germline variants in prostate cancer and implications for current genetic testing guidelines. *JAMA Oncol* 2019; 5:523-8.
14. Castro E, Goh C, Leongamornlert D, et al. Effect of BRCA mutations on metastatic relapse and cause-specific survival after radical treatment for localised prostate cancer. *Eur Urol* 2015; 68:186-93.
15. Carlo MI, Giri VN, Paller CJ, et al. Evolving intersection between inherited cancer genetics and therapeutic clinical trials in prostate cancer: a white paper from the Germline Genetics Working Group of the Prostate Cancer Clinical Trials Consortium. *JCO Precis Oncol* 2018; 2018.
16. Zon RT, Goss E, Vogel VG, et al. American Society of Clinical Oncology policy statement: the role of the oncologist in cancer prevention and risk assessment. *J Clin Oncol* 2009; 27:986-93.
17. Mohler JL, Armstrong AJ, D'Amico AV, et al. NCCN Clinical Practice Guidelines in Oncology Prostate Cancer, Version 1.2018, Available at: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed: December 1, 2018.
18. Parent EE, Schuster DM. Update on (18)F-fluciclovine PET for prostate cancer imaging. *J Nucl Med* 2018; 59:733-9.
19. Cantiello F, Crocerossa F, Russo GI, et al. Comparison between ^{64}Cu-PSMA-617 PET/CT and ^{18}F-choline PET/CT imaging in early diagnosis of prostate cancer biochemical recurrence. *Clin Genitourin Cancer* 2018; 16:385-91.
20. Miyahira AK, Pienta KJ, Morris MJ, et al. Meeting report from the Prostate Cancer Foundation PSMA-directed radionuclide scientific working group. *Prostate* 2018; 78:775-89.
21. Giri VN, Knudsen KE, Kelly WK, et al. Role of genetic testing for inherited prostate cancer risk: Philadelphia Prostate Cancer Consensus Conference 2017. *J Clin Oncol* 2018; 36:414-24.
22. National Institutes of Health, National Human Genome Research Project. The Genetic Information Nondiscrimination Act of 2008, Available at: https://www.genome.gov/27568492/the-genetic-information-nondiscrimination-act-of-2008. Accessed: December 3, 2018.
23. National Comprehensive Cancer Network. Prostate Cancer, Available at: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed: December 3, 2018.
24. National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast and Ovarian, Available at: https://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf. Accessed: December 3, 2018.

25. Riley BD, Culver JO, Skrzynia C, et al. Essential elements of genetic cancer risk assessment, counseling, and testing: updated recommendations of the National Society of Genetic Counselors. *J Genet Couns* 2012; 21:151-61.
26. Robson ME, Bradbury AR, Arun B, et al. American Society of Clinical Oncology policy statement update: genetic and genomic testing for cancer susceptibility. *J Clin Oncol* 2015; 33:3660-7.
27. Sanda MG, Cadeddu JA, Kirkby E, et al. Clinically localized prostate cancer: AUA/ASTRO/SUO guideline. Part I: risk stratification, shared decision making, and care options. *J Urol* 2018; 199:683-90.
28. Hoskovec JM, Bennett RL, Carey ME, et al. Projecting the supply and demand for certified genetic counselors: a Workforce study. *J Genet Couns* 2018; 27:16-20.
29. Stoll K, Kubendran S, Cohen SA. The past, present and future of service delivery in genetic counseling: keeping up in the era of precision medicine. *Am J Med Genet C Semin Med Genet* 2018; 178:24-37.
30. World Health Organization. Genomic resource centre. Continuing education for health professionals, Available at: https://www.who.int/genomics/professionals/education/en/. Accessed: December 3, 2018.

Supplemental Appendix 1

Survey Questions and Germline Genetic Testing-Related Therapeutic Clinical Trials

1. What are your current personal practices around genetics services?
2. If you practice a combination of approaches, very briefly, how would you describe your general approach for an individual patient?
3. What prostate cancer patient population(s) are you currently considering for germline genetic testing? Select all that apply.
   a. Men with metastatic PCa (all)
   b. Men with metastatic PCa (trial candidates)
   c. Men with metastatic PCa (with family history of cancer)
   d. Men with high-risk localized or nonmetastatic PCa (all)
   e. Men with high-risk localized or nonmetastatic PCa (trial candidates)
   f. Men with high-risk localized or nonmetastatic PCa (with family history of cancer)
   g. PCa patients with family history of PCa and other cancers
   h. Other criteria (see next question)
4. If you are testing a combination of the groups listed above, very briefly, how would you describe your decision process for an individual patient?
5. What is your personal/institutional mechanism or system to integrate germline results with therapeutic clinical trials?
6. What is your personal/institutional mechanism for cascade testing of pathogenic/likely pathogenic germline mutation carriers?
7. Cascade genetic testing refers to offering genetics referral to relatives such as siblings and children of patients found to carry a germline mutation (pathogenic variant) in a cancer risk gene. This might provide valuable information for family members regarding their own risk and options for cancer screening and prevention. Is the cascade genetic testing process in your practice systematized to attempt to capture screening for other cancers and to facilitate cascade testing of family members?
8. What is your general approach to germline cancer predisposition testing? (If you select more than one, please explain further in the question that follows.)
   a. Specific individual genes (eg, *BRCA1*, *BRCA2*)
   b. Limited prostate cancer-specific panel
   c. Expanded cancer panel (eg, Lynch and *BRCA1/2* and hereditary breast and ovarian cancer genes)
   d. Comprehensive, pan-cancer panel
   e. Clinical trial-focused panel
   g. Reflex, single-site if tumor sequencing suggests germline finding
9. Please add any comments or details about your approach here.
10. Do you have any clinical trials around the delivery of genetic testing at your institution open or anticipated? (See Responses in Table 4.)
11. Do you have suggestions for patient/family resources to recommend to patients for more information?
12. What would be most immediately helpful to you as a resource for germline genetics that the PCCTC Working Group can help develop?
13. List any specific concerns, frustrations, worries, barriers, and challenges you would like to share around germline genetics and prostate cancer.
14. What is your name/institution?

Germline and Somatic Mutations in Prostate Cancer for the Clinician

Heather H. Cheng, MD, PhD[a,b]; Alexandra O. Sokolova, MD[a,b]; Edward M. Schaeffer, MD, PhD[c]; Eric J. Small, MD[d]; and Celestia S. Higano, MD[a,b]

ABSTRACT

It is increasingly important for clinicians involved in the management of prostate cancer to understand the relevance of heritable (germline) mutations that, for select patients, affect prostate cancer risk and cancer biology, and acquired (somatic) mutations that occur in prostate cancer cells. In the advanced disease setting, mutations in homologous recombination repair genes (eg, *BRCA1*, *BRCA2*, *ATM*, *CHEK2*, *PALB2*) suggest candidacy for platinum chemotherapy and PARP inhibitor trials. Similarly, microsatellite instability and mismatch repair deficiency, which may arise in the setting of *MLH1*, *MSH2*, *MSH6*, and *PMS2* mutations, suggest potential vulnerability to PD-1 inhibitors. Germline genetic testing has potential importance in the treatment and assessment of familial risk, and tumor-directed somatic sequencing may guide treatment decision-making. This review provides clinicians with knowledge of basic genetic terminology, awareness of the importance of family history of cancer (not limited to prostate cancer), contrasts between the different but potentially related objectives of germline versus somatic testing of tumor tissue, and indications for genetic counseling. Specific clinical scenarios, objectives of testing, and nature of the assays are reviewed. Germline and somatic mutations of known and potential relevance to prostate cancer are discussed in the context of treatment options, and algorithms to assist clinicians in approaching this area are proposed.

J Natl Compr Canc Netw 2019;17(5):515–521
doi: 10.6004/jnccn.2019.7307

[a]Division of Medical Oncology, University of Washington, and [b]Division of Clinical Research, Fred Hutchinson Cancer Research Center, Seattle, Washington; [c]Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, Illinois; and [d]Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco, California.

Expansion of genomic technologies and declining costs of next-generation sequencing (NGS) have led to rapid changes in germline and somatic genetic testing that must be considered in everyday clinical practice. Similar technology is used in direct-to-consumer "recreational" testing for understanding genealogic origins from an individual's DNA. Tests for primary prostate cancer to determine risk of recurrence and inform decisions regarding active surveillance are addressed elsewhere.[1–3] This review focuses on testing ordered by medical providers to determine heritable risk of cancer and guide treatment options in the advanced disease setting, provides a framework for understanding current options and uses for genetic testing, and considers data supporting genetic testing recommendations in the latest version of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Prostate Cancer, version 2.2019 (in this issue).[4]

Germline DNA refers to the constitutional DNA of an individual resulting from the unique combination of genetic material, half from mother (egg) and half from father (sperm). (A list of key terms and definitions is provided in supplemental eTable 1, available with this article at JNCCN.org). Germline DNA is present in every cell of the body, and specific genetic changes have a 50/50 chance of being passed on to biologic children. Germline genetic testing can identify presence of inherited pathogenic variants (also called *mutations*) in genes associated with cancer risk. Testing can be performed on lymphocyte DNA from blood or a combination of lymphocyte and buccal cells from saliva, because germline DNA is nearly identical in all nucleated cells of an individual. Identification of a germline mutation associated with cancer susceptibility should involve a genetic counselor to ensure that medical, psychologic, legal, and ethical consequences for the patient and relatives are explained. Germline testing also can have important implications regarding treatment options for some patients with cancer.

In prostate cancer, the percentage of patients with germline mutations in DNA repair genes ranges from

See JNCCN.org for supplemental online content.

4.6% in localized disease to 11.8% to 16.2% in metastatic disease.[5,6] Patients with a strong pattern of cancers found on a comprehensive family history should be evaluated by a genetic counselor, who may recommend specific tests (Figure 1). In addition, if a germline mutation is identified, genetic counselors ensure appropriate education and testing for family members who may also carry the same gene mutation, a process known as "cascade genetic testing."

Sequencing DNA for tumor-acquired genetic changes (also referred to as *somatic mutations*) requires prostate tumor material: cancer-containing biopsies, surgical material, or, in some cases, circulating tumor cells or circulating tumor DNA (ctDNA) in the blood. Testing of tumor tissue from primary or metastatic sites or blood may help guide treatment options in the advanced disease setting. A number of specific mutations are summarized in Table 1, although the base of knowledge is evolving rapidly.

Somatic mutations observed in tumor tissue may change over time due to genetic instability and selective pressure from therapy. Thus, repeat testing of tumor DNA may be appropriate during the disease course. Findings in archival primary tissue obtained years earlier may differ from those in a metastatic site, although detection of certain relevant mutations is possible early in tumorigenesis. Other potential limitations include

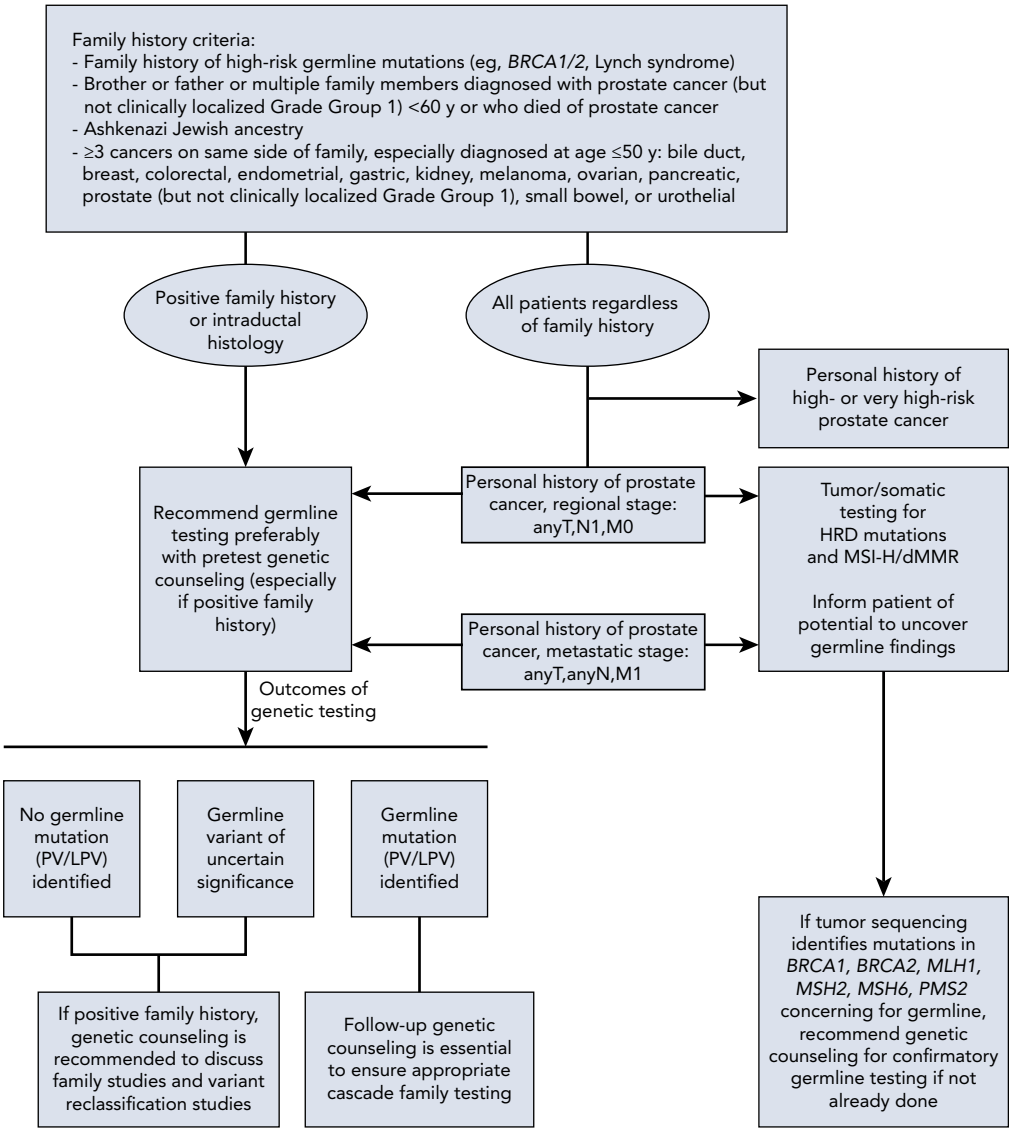


Figure 1. Algorithm for inherited/germline and tumor/somatic mutation testing in men diagnosed with prostate cancer.
Abbreviations: dMMR, mismatch repair deficiency; HRD, homologous recombination DNA repair; MSI-H, microsatellite instability-high; PV/LPV, pathologic variant or likely pathologic variant.

Table 1. Genes With Established or Emerging Potential Clinical Actionability, Germline vs Somatic

Gene	Association With Increased PC Risk	Prevalence of Germline Mutations in mPC[5]	Prevalence of Germline Mutations in PC With Clinical Suspicion[11]	Consideration of DNA-Damaging Agents: PARPi Trials, Platinum[40]	Consideration of Immune Checkpoint Inhibitors: PD-1 Inhibitors
ATM	X	1.6%	2.0%	X	
ATR		0.3%	Not evaluated		
BRCA1	X	0.9%	0.7%	X	
BRCA2	X	5.4%	4.7%	X	
BRIP1		0.2%	0.3%		
CDK12 (somatic only)		—	—		X
CHEK2	X	1.9%	2.9%	X	
FAM175A		0.2%	Not evaluated		
FANCA		—	Not evaluated	X	
HOXB13 (germline only)	X	Not evaluated	1.1%		
MLH1	X	—	0.06%		X
MRE11A		0.14%	Not evaluated		
MSH2	X	0.14%	0.69%		X
MSH6	X	0.14%	0.45%		X
NBN	[a]	0.3%	0.32%	X	
PALB2	[a]	0.4%	0.56%	X	
PMS2	X	0.3%	0.54%		X
RAD51C		0.14%	0.21%		
RAD51D		0.4%	0.15%		

Abbreviations: mPC, metastatic prostate cancer; PARPi, PARP inhibitors; PC, prostate cancer.
[a]Emerging/Limited data.

variance in tumor content and purity, and sensitivity and specificity of detecting tumor-specific mutations. Tumor-based testing has the potential to identify germline mutations that have implications for inherited cancer predisposition.[7,8] Tumor testing should never be used to substitute for germline testing because of the risk for false-positives and false-negatives due to variation in bioinformatics and reporting between commercially available tests. If somatic testing identifies a mutation in a gene associated with cancer predisposition (eg, *BRCA2*), referral to a genetic counselor for dedicated, confirmatory germline testing is indicated.

Family and Personal History of Cancer

Family history of cancer remains a foundation of genetic risk assessment, and inquiring about prostate and non-prostate cancers is critical to a complete assessment for possible inherited cancer risk (supplemental eTable 2).[5] In particular, cancers of the breast (especially in men or those diagnosed at a young age), ovary, pancreas, and melanomas should be noted, given their known association with mutations in *BRCA1/2*.[9] However, other cancers, such as mesothelioma, should also be noted.[10] Importantly, family history is necessary but not sufficient for identifying all germline carriers.[5]

In a recent study of 3,607 men diagnosed with prostate cancer who underwent genetic testing between 2013 and 2018, 17.2% were found to have germline mutations and 37% would not have met criteria for testing from the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian.[9] However, the dates spanned a period when guidelines were changing (consideration of genetic testing in individuals with a personal history of metastatic prostate cancer was not incorporated until 2017), and therefore the tested population was likely influenced by clinical suspicion based on family history even if they did not meet contemporaneous testing guidelines.[11] The argument that all men with prostate cancer should be tested is thought-provoking, but cost-effectiveness and actionability of widespread genetic testing in early, low-risk prostate cancer settings without other risk factors remain unclear, and short-term unintended consequences include clinical confusion and low-yield depletion of limited genetic counseling resources.

In contrast, clinical predictors of germline status, such as metastatic stage[5] or intraductal histology,[12,13]

emerging data about ductal histology,[14,15] and/or history of second or multiple primary cancers at younger age[16] may help prioritize candidates for testing, because each has been independently associated with the presence of germline DNA repair mutations. The biochemically recurrent population is heterogeneous, although application of advanced modern imaging such as C-11 choline and F-18 fluciclovine PET scans may help distinguish patients with indolent versus occult metastatic disease. Figure 1 illustrates the interaction between clinical disease features, family history, and pathology to determine who should be offered germline and/or somatic testing and genetic counseling.[4]

Genetic Counseling

Genetic counselors play an essential role in many aspects of the genetic testing process, but particularly in educating patients and family members, deciding on appropriate testing when there is strong family history, guiding accurate communication of medical information to family, and addressing psychosocial aspects of testing.

Risk assessment and pretest genetic counseling have been performed traditionally by genetic counselors, but access and long wait times can hamper time-sensitive testing that may inform treatment options in advanced disease. Ongoing studies are exploring novel delivery models for genetic services to balance time sensitivity with responsibility for informed consent, pretest education, and posttest follow-up (ClinicalTrials.gov identifiers: NCT02987543, NCT3328091, and NCT03503097).

Figure 1 illustrates the points in care at which genetic counseling is essential: (1) when there is a strong family history of cancer to ensure appropriate testing is ordered and that posttest communication to family is accurate; (2) after a germline pathogenic variant (mutation) is identified to ensure cascade testing; (3) when somatic testing uncovers a mutation that is potentially germline in nature; or (4) if the patient displays any indication of stress, distress, or unanswered questions. Providers should work closely with their genetics colleagues to develop systems that address patient needs with thoughtful stewardship of local genetics resources.

Genetic Testing

Choice of which germline test to use is beyond the scope of this review, although a number of commercial tests are available and typically use blood or saliva. There is variation in insurance coverage and out-of-pocket costs, although with assistance programs and competitive pricing, patient costs can often be limited to several hundred dollars or less. If genetic testing is being performed in the context of advanced prostate cancer, *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *CHEK2*, *MLH1*, *MSH2*, *MSH6*, and *PMS2* should be included due to potential treatment implications, although this list is expected to be refined over time. In specific research or clinical contexts, a larger gene panel may be appropriate. For example, *HOXB13* is a prostate cancer risk gene that does not have clear therapeutic implications in advanced disease at this time, but which should be included if heritable prostate cancer risk is part of the question.[4] Similarly, the gene list to consider may be larger for a somatic tumor gene panel and extend beyond cancer risk genes.

Potential outcomes for germline testing include identification of a mutation (pathogenic or likely pathogenic variant), which may suggest additional prostate cancer treatment options and clinical trials and inform risk of other cancers. This result would also indicate a 50/50 chance that first-degree relatives inherited the same risk gene and thus would prompt a recommendation for the patient to share this information (including a copy of test results) with relatives and for referral of family members to genetic counseling for cascade genetic testing. Single-site testing for a specific mutation is typically covered by insurance and is less expensive.

Another potential outcome is a variant of uncertain significance (VUS), which indicates that available data in the field were insufficient to characterize the finding as either benign or pathogenic at the time of test interpretation. A VUS result should not be used to direct clinical management. Research studies are available to help reclassify VUS, and these can be discussed with a genetic counselor.[17] In one study, 7.7% of VUS results were reclassified: 91% as benign/likely benign and 9% as pathogenic/likely pathogenic.[18]

An outcome could also be that no mutations were identified (a benign result). Failure to identify a single, inherited cancer risk–associated mutation does not obviate an increased risk of prostate cancer to family members if there is a strong family history. If testing is negative (benign, with no mutations) or identifies a VUS, the clinical family history should be used to guide cancer screening for family members. Although tempting, VUS—including and especially in *BRCA1/2*—should not be used for medical management, although follow-up with genetic counseling and consideration of research opportunities, such as registries and variant reclassification studies, are encouraged.

Individuals found to have germline pathogenic (or likely pathogenic) variants must see a genetic counselor for counseling, guidance on communication to family, and appropriate cascade genetic testing that extends genetic testing to other family members (https://www.nsgc.org/findageneticcounselor). Providers should also be aware that telehealth-, phone-, and new technology-based genetic counseling services may be an additional option for patients.

Genes With Germline and Somatic Actionability

Prostate Cancer Risk

For germline *BRCA2* mutation carriers, the relative risk of developing prostate cancer by age 65 years is estimated to be 2.5- to 8.6-fold compared with noncarriers.[19] In a recent study, lifetime risk of prostate cancer by age 80 years was reported between 19% and 61%, and 7% and 26% for carriers of *BRCA2* and *BRCA1* mutations, respectively.[20] Retrospective studies have shown that men with *BRCA2* mutations present at a younger age with higher Gleason grade tumors, higher rates of nodal involvement and distant metastases at diagnosis, and higher prostate cancer–specific mortality.[21,22] *BRCA1*,[23] *ATM*,[24] *CHEK2*,[25,26] and *PALB2*[27] also are involved in homologous recombination DNA repair and have been associated with increased prostate cancer risk, although these germline mutations have fewer data available and suggest less apparent relative risk of developing prostate cancer compared with *BRCA2*.[5,28] Germline mutations in the mismatch repair (MMR) genes *MLH1*, *PMS2*, *MSH2*, and *MSH6* are associated with Lynch syndrome, an inherited condition that predisposes individuals to an increased risk of developing many different types of cancers, including colorectal, endometrial, and gastrointestinal, often at a young age.[29] Several studies suggest a modest increased risk of prostate cancer in patients with Lynch syndrome,[30,31] and germline MMR gene mutations have been seen in the metastatic setting.[5] *HOXB13* G84E is a germline variant associated with increased risk of developing prostate cancer, but this variant is not clearly associated with increased disease aggressiveness nor should it influence treatment decision-making.[32–34] Emerging data suggest that *NBS1* (also called *NBN*),[35] *FANCA*,[36] and other DNA repair genes are associated with increased prostate cancer risk and choice of treatment, but further studies are needed before clinical action is warranted.

Screening Recommendations for Carriers of Pathogenic Germline Mutations

Screening recommendations have not been established for men with pathogenic germline mutations associated with increased prostate cancer risk. The ongoing IMPACT study is evaluating the role of targeted prostate-specific antigen (PSA) screening in men with *BRCA1/2* mutations (ClinicalTrials.gov identifier: NCT00261456). Preliminary results support yearly PSA screening in men with *BRCA2* mutations aged 40 to 69 years.[37] NCI's recently opened Men at High Genetic Risk for Prostate Cancer trial incorporates annual PSA testing and regular digital rectal examination and prostate MRI (NCT03805919). If clinical trial participation is not available, annual PSA measurement for carriers of high-risk mutations should begin at age 40 years (Figure 2). Men with PSA levels greater than the median age-adjusted PSA ranges[3,38,39] may consider prostate biopsy, which may be MRI/ultrasound fusion–guided.

Therapeutic Implications of Genetic Testing

Prostate tumors can now be sequenced for mutations that may offer molecularly targeted therapeutic options.[4] Archival tissue from the primary is often considered acceptable for studies of targeted agents when the biomarker in question is present, but archival tissue from a patient who has had multiple therapies may not reflect current tumor DNA status. Contemporary sampling of metastatic disease sites or cell-free ctDNA or circulating tumor cells may be more informative, although uninformative somatic testing, false-negatives, and limitations due to tumor purity must also be considered. Studies suggest that concordance with metastatic tissue can be good,[40] and that clinical selection and the timing of ctDNA draw at progression may improve diagnostic yield.[41]

Recent studies have resulted in major changes to consideration of germline testing in some patients with prostate cancer.[5,6,13,15] Germline genetic testing is now recommended for all men with a family history of prostate cancer or intraductal histology and/or high- or very high-risk regional or metastatic prostate cancer.[4] The decreasing cost of germline panel testing has made it more feasible to follow these guidelines for testing, although substantial issues remain regarding disparities in insurance coverage and access to genetic counseling.

The standards for somatic testing and reporting are less established than those for germline testing. Rapid changes in assays and clinical trials in progress make it difficult to recommend specific assays. A number of NGS sequencing panels are available and FDA-approved for somatic testing

For men with personal history of *BRCA1/2* mutation, Lynch syndrome, or mutations (ie, pathogenic variants) in prostate cancer-associated risk genes:

- Begin screening at age 40 y.
- Annual PSA and DRE.
- Men with a PSA level above the median for their age group are at higher risk for prostate cancer and aggressive prostate cancer. The higher above the median, the greater the risk.
- If PSA level is below age-adjusted median and no other indication for biopsy, repeat screening in 12 months.
- If PSA level is above age-adjusted median, recheck PSA in 6–12 months; if increased, consider extended pattern biopsy with mpMRI or TRUS-guidance.
- Upper limit age-adjusted median range PSA[38,39]:
  - Aged ≤49 y, PSA >1.5 ng/mL
  - Aged 50–59 y, PSA >2.0 ng/mL
  - Aged 60–69 y, PSA >2.5 ng/mL

Figure 2. Recommendations for prostate cancer early detection in carriers of high-risk mutations.

Abbreviations: DRE, digital rectal examination; mpMRI, multiparametric MRI; PSA, prostate-specific antigen; TRUS, transrectal ultrasound.

in CLIA-certified laboratories. Currently, somatic testing for homologous recombination gene mutations and microsatellite instability (MSI) and MMR deficiency (dMMR) should be considered due to potential treatment implications. In addition, some somatic NGS assays may also report alterations that, although investigational, may inform clinical trial candidacy: androgen receptor amplifications, *PTEN* deletions, PI3K/Akt/mTOR pathway alterations, and *TMPRSS2-ERG* gene fusions.

The definition of actionability for specific gene mutations in prostate cancer is emerging, and currently at least 2 classes of gene mutations should be considered (Table 1). Tumor and/or germline mutations in genes such as *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *FANCA*, *RAD51D*, and *CHEK2* may suggest candidacy for early use of platinum-based chemotherapy[42,43] or enrollment in clinical trials testing PARP inhibitors,[44] such as olaparib and rucaparib, which have been granted breakthrough designation by the FDA. Ongoing clinical trials are evaluating a number of PARP inhibitors for metastatic castration-resistant prostate cancer (mCRPC) and earlier disease states (ClinicalTrials.gov identifiers: NCT02854436, NCT02975934, NCT02987543, and NCT03148795). Retrospective and prospective studies to date have not shown that any FDA-approved treatment of mCRPC should be withheld from men with advanced prostate cancer and germline mutations.[45–47]

Tumor DNA evaluation for high MSI (MSI-H) or dMMR can be determined using immunohistochemistry or NGS methods demonstrating loss of function of *MLH1*, *MSH2*, *MSH6*, or *PMS2*, and is ideally validated for prostate cancer.[48,49] Identification of tumor MSI-H or dMMR indicates potential eligibility for pembrolizumab in later lines of therapy for advanced disease.[4]

Importance of the Molecular Tumor Board

Because approaches to NGS testing of tumors have changed and continue to evolve quickly, interpretation of results for the busy clinician may be challenging. Many institutions have instituted molecular tumor boards in which relevant clinical information is presented alongside results of germline and/or somatic testing and is reviewed by a multidisciplinary team. These tumor boards should include expert interpretation of data by a molecular pathologist, medical oncologist with disease-specific expertise, and genetic counselor, and may also include radiation and surgical oncologists. Such molecular tumor boards are increasingly available at comprehensive cancer centers with consultation for or participation by outside physicians because molecular pathology expertise is not yet widely available.

Conclusions

A summary of important points is available in eTable 3. Information about heritable (germline) and tumor-acquired (somatic) mutations has increasing importance in the management of men with prostate cancer. Germline data can inform both patient and family risk for prostate and other cancers and drive more aggressive screening in men at high risk of developing prostate cancer. Somatic testing is performed to determine whether the tumor has actionable targets for therapy, and prior knowledge of germline mutations can help in the interpretation of the results. Molecular tumor boards are needed to best interpret results and to direct clinical management and trial opportunities for providers and patients. Partnership with genetic counselors is needed to assist patients and relatives with decisions regarding genetic testing, interpretation, and follow-up cascade testing for family members. Clinicians should be aware of how to integrate genomic testing into treatment paradigms, because this field is rapidly evolving.

Submitted January 30, 2019; accepted for publication April 2, 2019.

Disclosures: Dr. Cheng has disclosed that she receives grant/research support from Clovis Oncology, Janssen, Medivation, Sanofi, and Astellas. Dr. Sokolova has disclosed that she has no financial interests, arrangements, affiliations, or commercial interests with the manufacturers of any products discussed in this article or their competitors. Dr. Schaeffer has disclosed that he is a scientific advisor for AbbVie and Opko. Dr. Small has disclosed that he has stock options in Fortis Therapeutics and Harpoon Therapeutics; and receives honoraria from Janssen; and is a scientific advisor for Janssen and Fortis. Dr. Higano has disclosed that she receives grant/research support from Aragon, Astellas, AstraZeneca, Bayer, Emergent Biosolutions, Medivation, Hoffman LaRoche, and Pfizer, and is a scientific advisor for Bayer, Blue Earth Diagnostics, Clovis Oncology, Ferring, Hinova, and Janssen.

Correspondence: Heather H. Cheng, MD, PhD, Division of Medical Oncology, University of Washington, 825 Eastlake Avenue East, Seattle, WA 98109. Email: hhcheng@uw.edu

References

1. Loeb S, Ross AE. Genomic testing for localized prostate cancer: where do we go from here? Curr Opin Urol 2017;27:495–499.
2. Boström PJ, Bjartell AS, Catto JW, et al. Genomic predictors of outcome in prostate cancer. Eur Urol 2015;68:1033–1044.
3. Loeb S, Carter HB, Catalona WJ, et al. Baseline prostate-specific antigen testing at a young age. Eur Urol 2012;61:1–7.
4. Mohler JL, Antonarakis ES, Armstrong AJ, et al. NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer. Version 2.2019. Accessed March 15, 2019. To view the most recent version, visit NCCN.org.
5. Pritchard CC, Mateo J, Walsh MF, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med 2016;375:443–453.
6. Castro E, Romero-Laorden N, Del Pozo A, et al. PROREPAIR-B: a prospective cohort study of the impact of germline DNA repair mutations on the outcomes of patients with metastatic castration-resistant prostate cancer. J Clin Oncol 2019;37:490–503.
7. Mandelker D, Zhang L, Kemel Y, et al. Mutation detection in patients with advanced cancer by universal sequencing of cancer-related genes in tumor and normal DNA vs guideline-based germline testing. JAMA 2017;318:825–835.
8. Cheng HH, Klemfuss N, Montgomery B, et al. A pilot study of clinical targeted next generation sequencing for prostate cancer: consequences for treatment and genetic counseling. Prostate 2016;76:1303–1311.

9. Daly MB, Axilbund JE, Buys S, et al. Genetic/familial high-risk assessment: breast and ovarian. J Natl Compr Canc Netw 2010;8:562–594. To view the most recent version, visit NCCN.org.
10. Panou V, Gadiraju M, Wolin A, et al. Frequency of germline mutations in cancer susceptibility genes in malignant mesothelioma. J Clin Oncol 2018;36:2863–2871.
11. Nicolosi P, Ledet E, Yang S, et al. Prevalence of germline variants in prostate cancer and implications for current genetic testing guidelines [published online February 7, 2019]. JAMA Oncol, doi: 10.1001/jamaoncol.2018.6760
12. Taylor RA, Fraser M, Livingstone J, et al. Germline BRCA2 mutations drive prostate cancers with distinct evolutionary trajectories. Nat Commun 2017;8:13671.
13. Risbridger GP, Taylor RA, Clouston D, et al. Patient-derived xenografts reveal that intraductal carcinoma of the prostate is a prominent pathology in BRCA2 mutation carriers with prostate cancer and correlates with poor prognosis. Eur Urol 2015;67:496–503.
14. Schweizer MT, Cheng HH, Tretiakova MS, et al. Mismatch repair deficiency may be common in ductal adenocarcinoma of the prostate. Oncotarget 2016;7:82504–82510.
15. Isaacsson Velho P, Silberstein JL, Markowski MC, et al. Intraductal/ductal histology and lymphovascular invasion are associated with germline DNA-repair gene mutations in prostate cancer. Prostate 2018;78:401–407.
16. Pilié PG, Johnson AM, Hanson KL, et al. Germline genetic variants in men with prostate cancer and one or more additional cancers. Cancer 2017;123:3925–3932.
17. Tsai GJ, Rañola JMO, Smith C, et al. Outcomes of 92 patient-driven family studies for reclassification of variants of uncertain significance [published online October 30, 2018]. Genet Med, doi: 10.1038/s41436-018-0335-7
18. Mersch J, Brown N, Pirzadeh-Miller S, et al. Prevalence of variant reclassification following hereditary cancer genetic testing. JAMA 2018;320:1266–1274.
19. Breast Cancer Linkage Consortium. Cancer risks in BRCA2 mutation carriers. J Natl Cancer Inst 1999;91:1310–1316.
20. Lecarpentier J, Silvestri V, Kuchenbaecker KB, et al. Prediction of breast and prostate cancer risks in male BRCA1 and BRCA2 mutation carriers using polygenic risk scores. J Clin Oncol 2017;35:2240–2250.
21. Castro E, Goh C, Leongamornlert D, et al. Effect of BRCA mutations on metastatic relapse and cause-specific survival after radical treatment of localised prostate cancer. Eur Urol 2015;68:186–193.
22. Castro E, Goh C, Olmos D, et al. Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. J Clin Oncol 2013;31:1748–1757.
23. Leongamornlert D, Mahmud N, Tymrakiewicz M, et al. Germline BRCA1 mutations increase prostate cancer risk. Br J Cancer 2012;106:1697–1701.
24. Helgason H, Rafnar T, Olafsdottir HS, et al. Loss-of-function variants in ATM confer risk of gastric cancer. Nat Genet 2015;47:906–910.
25. Näslund-Koch C, Nordestgaard BG, Bojesen SE. Increased risk for other cancers in addition to breast cancer for CHEK2*1100delC heterozygotes estimated from the Copenhagen general population study. J Clin Oncol 2016;34:1208–1216.
26. Wu Y, Yu H, Zheng SL, et al. A comprehensive evaluation of CHEK2 germline mutations in men with prostate cancer. Prostate 2018;78:607–615.
27. Erkko H, Xia B, Nikkilä J, et al. A recurrent mutation in PALB2 in Finnish cancer families. Nature 2007;446:316–319.
28. Na R, Zheng SL, Han M, et al. Germline mutations in ATM and BRCA1/2 distinguish risk for lethal and indolent prostate cancer and are associated with early age at death. Eur Urol 2017;71:740–747.
29. Cohen SA, Pritchard CC, Jarvik GP. Lynch syndrome: from screening to diagnosis to treatment in the era of modern molecular oncology [published online March 8, 2019]. Annu Rev Genomics Hum Genet, doi: 10.1146/annurev-genom-083118-015406
30. Raymond VM, Mukherjee B, Wang F, et al. Elevated risk of prostate cancer among men with Lynch syndrome. J Clin Oncol 2013;31:1713–1718.
31. Haraldsdottir S, Hampel H, Wei L, et al. Prostate cancer incidence in males with Lynch syndrome. Genet Med 2014;16:553–557.
32. Ewing CM, Ray AM, Lange EM, et al. Germline mutations in HOXB13 and prostate-cancer risk. N Engl J Med 2012;366:141–149.
33. Kote-Jarai Z, Mikropoulos C, Leongamornlert DA, et al. Prevalence of the HOXB13 G84E germline mutation in British men and correlation with prostate cancer risk, tumour characteristics and clinical outcomes. Ann Oncol 2015;26:756–761.
34. Giri VN, Knudsen KE, Kelly WK, et al. Role of genetic testing for inherited prostate cancer risk: Philadelphia Prostate Cancer Consensus Conference 2017. J Clin Oncol 2018;36:414–424.
35. Cybulski C, Wokołorczyk D, Kluźniak W, et al. An inherited NBN mutation is associated with poor prognosis prostate cancer. Br J Cancer 2013;108:461–468.
36. Tischkowitz M, Easton DF, Ball J, et al. Cancer incidence in relatives of British Fanconi Anaemia patients. BMC Cancer 2008;8:257.
37. Bancroft EK, Page EC, Castro E, et al. Targeted prostate cancer screening in BRCA1 and BRCA2 mutation carriers: results from the initial screening round of the IMPACT study. Eur Urol 2014;66:489–499.
38. Tang P, Sun L, Uhlman MA, et al. Initial prostate specific antigen 1.5 ng/ml or greater in men 50 years old or younger predicts higher prostate cancer risk. J Urol 2010;183:946–950.
39. Vickers AJ, Ulmert D, Sjoberg DD, et al. Strategy for detection of prostate cancer based on relation between prostate specific antigen at age 40-55 and long term risk of metastasis: case-control study. BMJ 2013;346:f2023.
40. Wyatt AW, Annala M, Aggarwal R, et al. Concordance of circulating tumor DNA and matched metastatic tissue biopsy in prostate cancer. J Natl Cancer Inst 2017;109:djx118.
41. Schweizer MT, Gulati R, Beightol M, et al. Clinical determinants for successful circulating tumor DNA analysis in prostate cancer [published online March 13, 2019]. Prostate, doi: 10.1002/pros.23778
42. Cheng HH, Pritchard CC, Boyd T, et al. Biallelic inactivation of BRCA2 in platinum-sensitive metastatic castration-resistant prostate cancer. Eur Urol 2016;69:992–995.
43. Pomerantz MM, Spisák S, Jia L, et al. The association between germline BRCA2 variants and sensitivity to platinum-based chemotherapy among men with metastatic prostate cancer. Cancer 2017;123:3532–3539.
44. Mateo J, Carreira S, Sandhu S, et al. DNA-repair defects and olaparib in metastatic prostate cancer. N Engl J Med 2015;373:1697–1708.
45. Mateo J, Cheng HH, Beltran H, et al. Clinical outcome of prostate cancer patients with germline DNA repair mutations: retrospective analysis from an international study. Eur Urol 2018;73:687–693.
46. Antonarakis ES, Lu C, Luber B, et al. Germline DNA-repair gene mutations and outcomes in men with metastatic castration-resistant prostate cancer receiving first-line abiraterone and enzalutamide. Eur Urol 2018;74:218–225.
47. Annala M, Struss WJ, Warner EW, et al. Treatment outcomes and tumor loss of heterozygosity in germline DNA repair-deficient prostate cancer. Eur Urol 2017;72:34–42.
48. Guedes LB, Antonarakis ES, Schweizer MT, et al. MSH2 loss in primary prostate cancer. Clin Cancer Res 2017;23:6863–6874.
49. Hempelmann JA, Lockwood CM, Konnick EQ, et al. Microsatellite instability in prostate cancer by PCR or next-generation sequencing. J Immunother Cancer 2018;6:29.

See JNCCN.org for supplemental online content.

JNCCN

National Comprehensive Cancer Network®

JOURNAL OF THE NATIONAL COMPREHENSIVE CANCER NETWORK

Supplemental online content for:

Germline and Somatic Mutations in Prostate Cancer for the Clinician

Heather H. Cheng, MD, PhD; Alexandra O. Sokolova, MD; Edward M. Schaeffer, MD, PhD; Eric J. Small, MD; and Celestia S. Higano, MD

J Natl Compr Canc Netw 2019;17(5):515–521

eTable 1. Key Terms and Definitions
Cascade testing: Genetic counseling and testing in blood relatives of individuals who have been identified with specific genetic mutations; may include screening, counseling, or referral for a patient with a relative who has tested positive for a genetic mutation.
CTC: Circulating tumor cells. Tumor cells from the circulation (blood) that can be enumerated, measured, and/or evaluated.
ctDNA: Circulating tumor DNA. Typically measured from cell-free DNA in the plasma.
DDR: DNA damage response pathways. Includes homologous recombination, MMR, base excision repair, and others.
dMMR: Deficiency in mismatch repair. Refers to the inability to use a mechanism of correcting errors in DNA by detecting and replacing bases in the DNA that are paired incorrectly (mismatched bases). dMMR in the tumor may be associated with susceptibility to treatments, such as immune checkpoint inhibitors.
Genetic counseling: The evaluation and understanding of a family's risk for an inherited medical condition. A genetic counselor is a healthcare professional with specialized training in medical genetics and counseling.
Genetic testing: Laboratory methods to evaluate DNA of an individual to identify increased risks of specific conditions (eg, cancer), select treatment, or determine response to treatment.
Germline DNA: Constitutional DNA that is inherited from mother and father, present in nucleated cells of the body, such as lymphocytes, and may be passed on to children. Some genes may be shared with siblings.
HRD: Homologous recombination deficiency. Refers to the inability to use a common mechanism of repairing harmful breaks that occur on both strands of DNA, known as doublestrand breaks, through genetic recombination. Examples: *BRCA2, BRCA1, PALB2.*
MSI-H: Microsatellite instability. MSI-high refers to microsatellite instability, a measure of dMMR. Can result from defects in genes such as *MLH1, MSH2, MSH6, or PMS2.*
NGS: Next-generation sequencing. High-throughput DNA sequencing technologies. Millions or billions of DNA strands can be sequenced in parallel to yield more throughput. Practically, this allows multiple genes to be tested at the same time in gene "panels."
Pathogenic variant: A genetic alteration that increases an individual's susceptibility or predisposition to a certain disease or disorder (eg, prostate cancer). Development of prostate cancer is more likely, but not certain, when such a variant (or mutation) is inherited.
Somatic DNA: Acquired mutations and genetic changes to the germline DNA. Often refers to tumor-associated genetic changes that are not heritable.
VUS: Variant of uncertain significance. Typically refers to a genetic change in germline DNA where there is insufficient information available to know if it causes an increased susceptibility to cancer or not.

Abbreviations: CTC, circulating tumor cells; ctDNA, circulating tumor DNA; dMMR, mismatch repair deficiency; HRD, homologous recombination deficiency; MMR, mismatch repair; MSI, microsatellite instability; MSI-H, microsatellite instability–high; NGS, next-generation sequencing; VUS, variant of uncertain significance.

eTable 2. Obtaining a Comprehensive Family History of Cancer

Detailed family history includes:

- Parents
- Children
- Siblings/Half siblings
- Grandparents and great-grandparents (specify maternal or paternal)
- Nieces and nephews
- Aunts and uncles (specify maternal or paternal)
- Cousins (specify maternal or paternal)
- Ethnicity/Country of origin
- Consanguinity

Minimal data for each cancer-affected relative:

- Current age and age at diagnosis (if not known exactly, decades can be helpful)
- Age at and cause of death (especially if cancer-related)
- Type of cancer (note multiple primaries)
- Results of any prior genetic testing

Resources for collecting family history:

- CDC My Family Health Portrait, https://phgkb.cdc.gov/FHH/html/index.html
- Cancer.net, https://www.cancer.net/sites/cancer.net/files/cancer_family_history_questionnaire.pdf
- NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal (see algorithm page HRS-A; available online at NCCN.org).

Abbreviation: CDC, Centers for Disease Control and Prevention.

eTable 3: Take-Home Points
• Germline DNA is inherited from both biologic parents and is present in all cells in the body. It does not change over time, therefore repeat testing will typically be of limited value.
• Somatic (tumor) DNA is comprised of germline genetic material with additional acquired mutations; however, somatic testing platforms may or may not report suspected germline mutations (pathogenic variants).
• Tumor testing may suggest the need for, but should never replace, dedicated germline testing.
• Tumor evolution over time means repeat somatic testing may be of value.
• Germline testing can identify increased risk for heritable cancers.
• Germline DNA may have therapeutic implications for some patients.
• Tumor sequencing can be performed to find actionable mutations that may have therapeutic implications in advanced disease.
• Germline mutation testing should be offered to patients with a family history of prostate other cancers, or those with a personal history of high- and very high-risk localized prostate cancer, regional, or metastatic disease.
• All patients with pathogenic germline mutations should be referred to a genetic counselor.
• When there is a strong family history, genetic counseling is recommended before genetic testing whenever possible.
• If germline testing is negative or inconclusive (ie, there is no known cancer associated with the identified mutation) but there is a strong family history for cancers, referral to genetic counseling is indicated.
• Variants of uncertain significance (VUS; including in *BRCA1/2*) should not be used for medical management.
• Tumor DNA analysis should be performed at a time when a new therapy is under consideration.
• Intraductal histology has a higher association with actionable tumor and germline mutations.
• Genetic counselors can be found at https://www.nsgc.org/findageneticcounselor.
• Carriers of the *BRCA1/2* mutation are at increased risk of prostate cancer before age 65 years, and prostate cancer in men with germline *BRCA2* mutations occurs earlier and is more likely to be associated with prostate cancer mortality.
• Men with germline *BRCA1/2* mutations may consider beginning shared decision-making about PSA screening at age 40 years and at annual intervals, factoring in age-adjusted median PSA values. Early detection clinical trials are recommended whenever possible.

European Journal of Cancer 114 (2019) 107–116

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Radium-223 in combination with docetaxel in patients with castration-resistant prostate cancer and bone metastases: a phase 1 dose escalation/randomised phase 2a trial

Michael J. Morris [a,*], Yohann Loriot [b], Christopher J. Sweeney [c], Karim Fizazi [b], Charles J. Ryan [d,1], Daniel H. Shevrin [e], Emmanuel S. Antonarakis [f], Neeta Pandit-Taskar [g], Désirée Deandreis [h,2], Heather A. Jacene [i,j], Hubert Vesselle [k], Oana Petrenciuc [l], Cindy Lu [l], Jorge A. Carrasquillo [g], Celestia S. Higano [m]

[a] *Department of Medicine, Memorial Sloan Kettering Cancer Center and Weill Cornell Medicine, New York, NY, USA*
[b] *Department of Cancer Medicine, INSERM U981, Gustave Roussy, Université Paris-Saclay, Villejuif, France*
[c] *Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA*
[d] *Department of Medicine and Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, CA, USA*
[e] *NorthShore Medical Group, NorthShore University Health System, Evanston Hospital Kellogg Cancer Center, Evanston, IL, USA*
[f] *The Sydney Kimmel Comprehensive Cancer Center, Johns Hopkins School of Medicine, Baltimore, MD, USA*
[g] *Department of Radiology, Molecular Imaging and Therapy Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA*
[h] *Nuclear Medicine and Endocrine Oncology, Institut Gustave Roussy, University of Paris Sud, Villejuif, France*
[i] *Department of Imaging, Dana-Farber Cancer Institute, Boston, MA, USA*
[j] *Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA*
[k] *Division of Nuclear Medicine, Department of Radiology, University of Washington, Seattle, WA, USA*
[l] *Department of Global Clinical Development, Bayer HealthCare Pharmaceuticals, Whippany, NJ, USA*
[m] *Department of Medicine, University of Washington, Fred Hutchinson Cancer Research Center, Seattle, WA, USA*

Received 29 January 2019; received in revised form 21 March 2019; accepted 2 April 2019
Available online 11 May 2019

* *Corresponding author*: Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA. Fax: +1 646 227 2417.
E-mail address: morrism@mskcc.org (M.J. Morris).
[1] Current address: Division of Hematology, Oncology and Transplantation, University of Minnesota, Minneapolis, MN, USA.
[2] Current address: Department of Medical Sciences, University of Turin Division of Nuclear Medicine, Turin, Italy.

https://doi.org/10.1016/j.ejca.2019.04.007

KEYWORDS
Castration-resistant prostate cancer;
Radium 223 dichloride;
Docetaxel;
Combination treatment

Abstract ***Purpose:*** Radium 223 dichloride (radium-223) is an alpha particle–emitting bone-directed therapy that prolongs overall survival in men with bone-predominant metastatic castration-resistant prostate cancer (mCRPC). Docetaxel is an antimicrotubule cytotoxic agent that improves survival in mCRPC. We investigated whether combining these potentially cross-sensitising agents to dually target tumour and bone would be safe and effective.
Patients and methods: Phase 1 was a dose escalation study to define a recommended phase 2 dose (RP2D) of docetaxel and radium-223. In phase 2a, patients were randomised 2:1 to the recommended combination regimen or docetaxel at a dose of 75 mg/m^2 every 3 weeks (q3w). Patients with bone-predominant mCRPC were eligible. End-points were safety, efficacy and treatment-related changes in serum and imaging biomarkers.
Results: Twenty patients were enrolled in phase 1; 53 patients were randomised in phase 2a: 36 to combination treatment and 17 to docetaxel alone. The RP2D for the combination was radium-223 55 kBq/kg every six weeks × 5 doses, plus docetaxel 60 mg/m^2 q3w × 10 doses. Febrile neutropenia was dose limiting. A higher rate of febrile neutropenia was seen in the docetaxel monotherapy arm (15% vs 0%); the safety profile of the treatment groups was otherwise similar. The combination arm had more durable suppression of prostate-specific antigen (median time to progression, 6.6 vs 4.8 months, respectively), alkaline phosphatase (9 vs 7 months) and osteoblastic bone deposition markers.
Conclusions: Radium-223 in combination with docetaxel at the RP2D was well tolerated. Exploratory efficacy data suggested enhanced antitumour activity for the combination relative to docetaxel alone. Comparative studies with end-points of clinical benefit are warranted. ClinicalTrials.gov number: NCT01106352.

1. Introduction

Prostate cancer is bone-tropic, rendering it particularly susceptible to treatments that target bone formation and osteoblastic activity. The cancer-induced abnormal bone metabolism that places patients at risk of death and morbidity can also be leveraged to deliver life-prolonging therapy.

Radium 223 dichloride (radium-223), a calcium mimetic alpha particle–emitting radiopharmaceutical, targets hydroxyapatite. It selectively accumulates in areas of increased bone turnover that surround metastatic lesions, where it emits four high-energy, short-range (<100 μm) alpha particles with resulting minimal radiation effects on the adjacent bone marrow [1,2]. In preclinical models, it reduces abnormal bone production, tumour burden and dysregulated bone deposition [3,4]. Clinically, radium-223—given at a dose of 55 kBq/kg every 4 weeks for 6 doses—prolongs life and the time to first symptomatic skeletal event in patients with bone-predominant metastatic castration-resistant prostate cancer (mCRPC) and no known visceral metastases [5].

Docetaxel is a chemotherapeutic agent that interferes with microtubule dynamics and has a radiosensitising effect [6]. Docetaxel given at a dose of 75 mg/m^2 every 3 weeks (q3w) in combination with prednisone prolongs life in patients with mCRPC [7].

We hypothesised that combining bone-targeted alpha radiation therapy with chemotherapy in patients with mCRPC might be an effective treatment approach, predicated on the concepts of multicompartment targeting and possible cross-sensitisation in bone lesions [8]. We conducted a phase 1/2a study to investigate this combination.

2. Patients and methods

2.1. Patients

Eligible patients had progressive mCRPC with ≥2 bone metastases, testosterone ≤50 ng/dL, Karnofsky Performance Status of ≥70%, life expectancy of ≥6 months and adequate organ functionality (white blood cell count ≥3 × 10^9/L, with an absolute neutrophil count ≥1.5 × 10^9/L, a platelet count ≥100 × 10^9/L and haemoglobin ≥10.0 g/dL; total bilirubin level ≤ upper limit of normal (ULN) and aspartate aminotransferase and alanine aminotransferase concentrations ≤1.5 × ULN; creatinine ≤1.5 × ULN and albumin >30 g/L). The patients needed to have had two consecutive prostate-specific antigen (PSA) increases at least one week apart, with a minimum value of 2 ng/mL at screening, or two or more new bone lesions when analysed by bone scintigraphy. Those patients on a first-generation androgen inhibitor needed to progress through a 4-week withdrawal. The exclusion criteria included the following: visceral metastases, defined as >2 lung metastases and/or liver metastases that were ≥2 cm in size, symptomatic nodal disease and malignant lymphadenopathy >3 cm in short-axis diameter. Patients should not have received >10

previous docetaxel doses or previous treatment with a bone-seeking radiopharmaceutical.

2.2. Study design

This two-part phase 1/phase 2a study, conducted at eight centres, seven in the United States and one in France, aimed to establish a recommended phase 2 dose (RP2D) of radium-223 in combination with docetaxel and to investigate safety and exploratory efficacy end-points at the RP2D.

In phase 1, between 9 and 18 patients were to be enrolled and treated according to a 3 + 3 design. The dose escalation scheme is shown in Fig. 1A. Dose-limiting toxicity (DLT) was assessed during the 6-week period after the first radium-223 injection. DLT was defined as absolute neutrophil count $<0.5 \times 10^9$/L for >7 days without fever despite granulocyte-colony stimulating factor support, grade ≥3 febrile neutropenia (after a protocol amendment), platelet count $<25 \times 10^9$/L for >7 days, grade ≥3 diarrhoea despite optimal medical management, grade ≥4 vomiting or constipation.

Radium-223 was started at a dose of 27.5 kBq/kg (according to the National Institute of Standards and Technology [NIST] 2016 update [9]), every six weeks (q6w), and could be escalated to 55 kBq/kg (according to NIST 2016 update [9]). The starting dose of docetaxel was 75 mg/m^2 q3w, with a planned reduction to 60 mg/m^2 in the event of DLT. We prioritised achieving full-dose radium-223 over full-dose chemotherapy in the dose escalation scheme, given that there are survival data using docetaxel as part of combination therapy at its step-down dose but no survival data using a lower dose of radium-223 [10]. Radium-223 was administered every other chemotherapy dose rather than monthly to optimise the likelihood of patient acceptance and compliance by having only one day of treatment per cycle, at a dosing interval known to have favourable clinical effects [11]. The number of doses was capped at five in an abundance of caution to protect long-term marrow integrity in the event of enhanced toxicity that would not be detected by blood count assessments during treatment. In all cohorts, docetaxel was to be administered every 3 weeks and was to be continued in the absence of progressive disease or unacceptable toxicity. Docetaxel and radium-223 were administered on the same day, with docetaxel administered first, followed by radium-223 as soon as practically feasible. Prednisone 5 mg was given orally twice daily, continuously. Dexamethasone premedication was given before docetaxel dosing as per each institution's practice. Growth factor support was allowed only as secondary prophylaxis.

In phase 2a, using a schedule generated by an independent statistician, patients were randomly assigned centrally 2:1, using a block randomisation scheme (block size of three), via an interactive voice response system, to combination therapy or docetaxel alone, respectively. A preplanned early stopping rule applied in the event of significant toxicity in the combination arm. The treatment period was a maximum of 30 weeks (10 doses of docetaxel), followed by 22 weeks of follow-up.

The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation E6, Good Clinical Practice. The protocol and all amendments were approved by the independent ethics committee/institutional review boards at each site, and written informed consent was obtained from the patients before any assessments were performed.

2.3. Assessments

Adverse events (AEs) were coded according to the Medical Dictionary for Regulatory Activities version 13.0. Severity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. The safety assessment period for AEs was from the start of study treatment to 6 weeks after the end of study treatment (8 weeks for serious AEs [SAEs]). Data on marrow sequelae and any second malignancies were collected up to 12 months after the start of study treatment. Exploratory efficacy assessments included on-treatment changes in bone alkaline phosphatase (bALP), total ALP (tALP), urinary C-telopeptide of type 1 (uCTX-1), N-terminal propeptide of procollagen type 1 (P1NP), pyridinoline cross-linked carboxyterminal telopeptide (ICTP), PSA and circulating tumour cells (CTCs).

2.4. Statistical considerations

The primary objectives were to establish a recommended dose of radium-223 combined with docetaxel and to investigate safety and explore efficacy at this dose level. The safety population included all patients who received treatment. To examine the antitumour effect of treatment in this exploratory study, the efficacy population comprised patients who received ≥40% (2 infusions) of the specified number of radium-223 doses (combination arm) or docetaxel doses (docetaxel arm) and had no major protocol violations (per protocol population). No formal statistical testing was planned.

Exploratory efficacy end-points included time to PSA progression, time to bALP progression, time to tALP progression, time to first radiographic or clinical progression based on Response Evaluation Criteria in Solid Tumours (RECIST) [12] version 1.1 and Prostate Cancer Working Group 2 (PCWG2) [13] definitions and overall survival. Time-to-event end-points were measured from the first dose of study treatment. For this report, progression-free survival (PFS) events are defined as radiographic or clinical progression or death. Medians

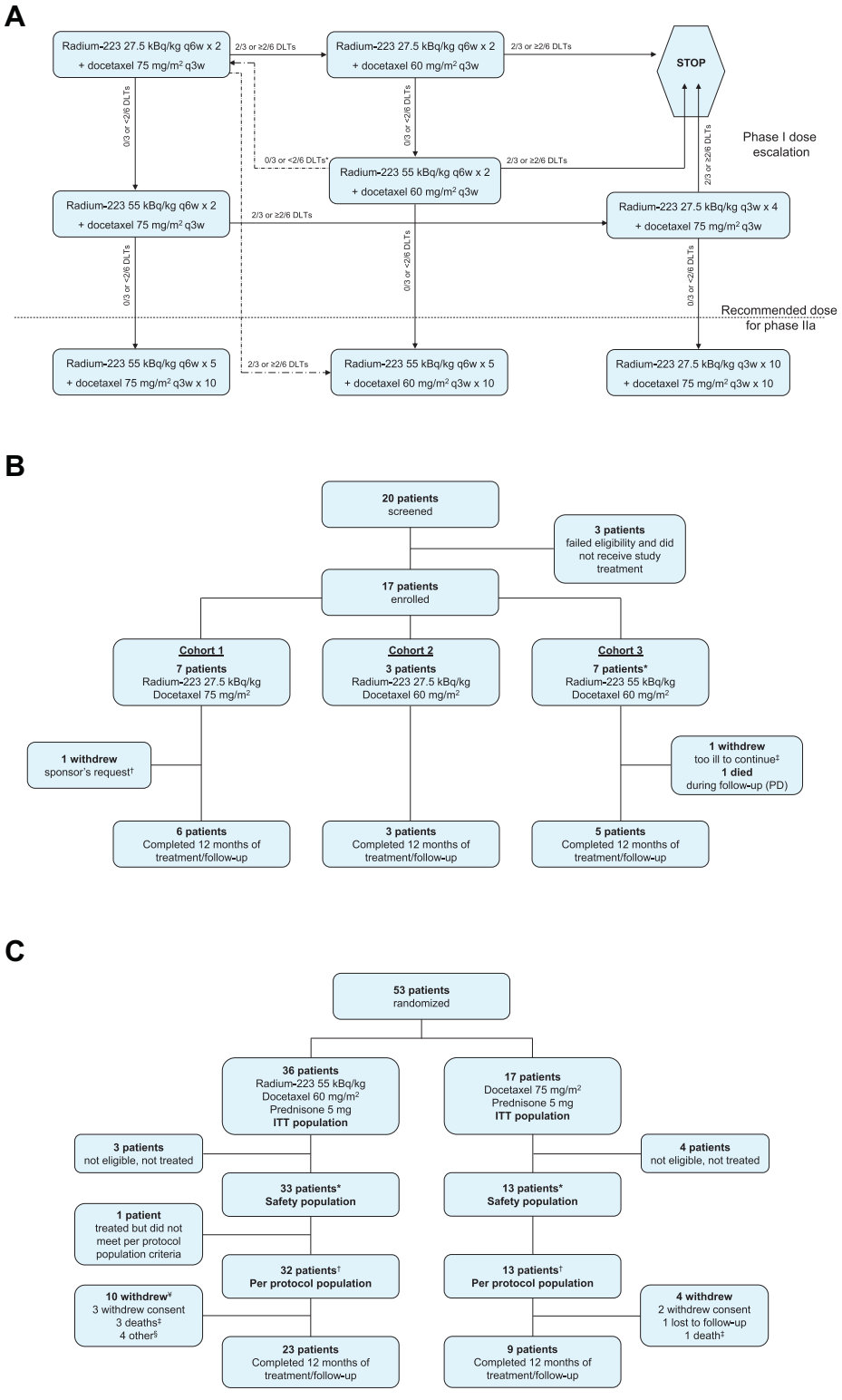


Fig. 1. Study profile. (A) Dose escalation scheme.*A return to the very first dose cohort could be considered in the event of 0/3 or <2/6 DLTs at 55 kBq/kg radium-223 + 60 mg/m^2 docetaxel q3w. If then 2/3 or ≥2/6 DLTs occurred at docetaxel 75 mg/m^2, the chosen regimen for the phase 2a cohort was to be radium-223 50 kBq/kg × 5 + docetaxel 60 mg/m^2 q3w × 10. (B) Phase 1 dose escalation cohorts. *One patient was replaced, unable to receive both combined doses of radium-223 and docetaxel because of docetaxel hypersensitivity. †Withdrew before receiving both doses of radium-223 to receive another treatment deemed necessary by the study sponsor. ‡Withdrew after receiving both doses of radium-223, too ill to attend the 12-month follow-up visit. (C) Phase 2a safety and efficacy cohort.*25 patients in the combination arm received all planned radium-223 doses, 20 patients in the combination arm and 5 patients in the docetaxel arm received all planned docetaxel doses; the dose for 4 patients in the docetaxel arm was stepped down to 60 mg/m^2. The study was completed through 12 months of follow-up from the start of treatment with 23 (70%) patients in the combination arm and 9 (69%) in the

for time-to-event variables were estimated using the Kaplan–Meier method. Changes in biomarkers over time were computed as the area under the bone marker curve. Based on the Lehmann alternative power function for a two-sided 0.05-level test, the planned 42 patients were to be randomised. Assuming for a given marker that the odds were 3:1 that a patient in the combination group had a greater area under the bone turnover curve relative to a patient in the docetaxel group, the power of the test was 0.78. *P* values for exploratory efficacy end-points have not been corrected for multiplicity of testing and are provided for information only.

3. Results

3.1. Phase 1 dose escalation

Seventeen patients were treated in the phase 1 dose escalation cohort, including three with visceral disease; patient disposition and baseline characteristics are summarised in Fig. 1B and Supplementary Table 1. No DLTs occurred among the first three patients treated at full-dose chemotherapy and half-dose radium-223 (27.5 kBq/kg), but two developed febrile neutropenia, which was not then specified as a DLT. The cohort was expanded to six patients; no DLTs or additional febrile neutropenia events were seen. Owing to febrile neutropenia in two of six patients, the docetaxel dose was reduced to 60 mg/m^2 in the second cohort, which also used radium-223 at a dose of 27.5 kBq/kg. No DLTs were seen in the first three patients enrolled in this cohort. Because it appeared that the docetaxel dose at 75 mg/m^2 was accounting for the neutropenic fevers, the radium-223 dose was escalated to 55 kBq/kg in the third cohort, holding the docetaxel dose at 60 mg/m^2. No DLTs were seen in the first three patients enrolled at this dose level. However, one patient developed grade 3 neutropenia and another developed grade 4 neutropenia, both without fever or infection. After reviewing the safety data, it was decided to add three more patients to this cohort. No DLTs occurred in these patients. The third cohort dose (55 kBq/kg radium q6w × 5 and 60 mg/m^2 docetaxel q3w × 10) was consequently selected as the RP2D to be administered over 30 weeks. Haematological treatment-emergent AEs (TEAEs) occurring in phase 1 are shown in Supplementary Table 2.

3.2. Phase 2a cohort

3.2.1. Patients and treatment

Between December 19, 2012, and April 7, 2014, 53 patients were randomly assigned to receive combination therapy with docetaxel 60 mg/m^2 and radium-223 55 kBq/kg q6w × 5 (n = 36) or docetaxel alone, at a standard dose of 75 mg/m^2 q3w × 10 (n = 17, Fig. 1C, Supplementary Fig. 1); seven patients were found not to be eligible and were not treated. Baseline characteristics were similar between treatment groups (Table 1). Seven (15%) of 46 eligible patients had visceral metastases at baseline, five in the combination arm and two in the docetaxel arm.

3.2.2. Treatment exposure

The patients in the combination arm received a cumulative median of 1187 mg of docetaxel (range, 250–1520), versus 1270 mg (range, 643–1600) in the docetaxel monotherapy arm. The median number of docetaxel doses was 10 (range, 2–11) in the combination arm and 9 (range, 4–10) in the monotherapy arm. The median number of radium-223 doses in the combination arm was 5 (range, 1–5).

In the combination therapy arm, radium-223 and docetaxel administration was delayed in two patients because of TEAEs (cellulitis and osteoporosis), with docetaxel administration delayed in a further five patients (because of back pain, pain in extremity; oral abscess; pneumonia; toothache; diarrhoea, dehydration, pleural effusion, acute respiratory failure and pneumonia). There were three dose delays because of TEAEs in the docetaxel arm (hypotension; influenza-like illness, cough and melaena; cellulitis). In the combination arm, radium-223 and docetaxel were discontinued in 4 of 33 (12%) patients because of TEAEs (unilateral blindness; cerebrovascular accident; pneumonitis; asthenia and back pain), and docetaxel was discontinued in a further two (6%) patients (peripheral neuropathy; asthenia). In the docetaxel arm, 3 of 13 (23%) patients discontinued treatment because of TEAEs (febrile neutropenia; interstitial lung disease; peripheral neuropathy).

3.2.3. Safety

TEAE and TESAE incidence in the phase 2a safety population is summarised in Table 2 and Supplementary Table 3. Notably, there was less toxicity of any grade seen with combination therapy than docetaxel alone for neutropenia, febrile neutropenia, fatigue, dyspnoea, arthralgia and nausea. However, combination therapy was associated with more diarrhoea and back pain. The incidence of grade 3 or 4 TEAEs was low in both arms (Table 2), with the exception of neutropenia. Febrile neutropenia occurred in two patients (one grade 3 and one grade 4) in the docetaxel arm and none in the combination arm; growth factors were used to prevent or resolve neutropenia in four patients in the combination arm and two

docetaxel arm. †Received at least 40% of drug dose, no protocol violation. ¥Including the one patient who was excluded from the per protocol population. ‡All deaths occurred during follow-up and were due to disease progression. §3 patients entered hospice, and 1 had disease progression. PD, progressive disease; DLT, dose-limiting toxicity; ITT, intention to treat; q3w, every 3 weeks; q6w, every 6 weeks.

Table 1
Baseline characteristics (phase 2a cohort).

Characteristic	Radium-223 + docetaxel $N = 33$	Docetaxel $N = 13$
Age, median (range), years	68 (49–82)	67 (55–82)
Weight, median (range), kg	87 (61–120)	78 (69–132)
Karnofsky Performance Status, median %, (range)	90 (70–100)	90 (70–100)
Albumin, median, g/L	43.0	43.0
Haemoglobin, median, g/L	122.0	121.0
PSA		
>ULN, *N* (%)	32 (97)	13 (100)
Median (range), µg/L	99 (3–1000)	43 (4–1042)
Total ALP		
>ULN, *N* (%)	20 (61)	10 (77)
Median (range), U/L	167 (62–1016)	186 (74–472)
Bone ALP		
>ULN, *N* (%)	23 (70)	11 (85)
Median (range), µg/L	36 (10–331)	47 (16–164)
LDH		
>ULN, *N* (%)	6 (18)	2 (15)
Median (range), U/L	191 (123–418)	190 (124–328)
Patients with visceral metastatic lesions, *N* (%)		
Any	5 (15)	2 (15)
Lung	1 (3)	1 (8)
Liver	0	0
Other	4[a] (12)	1[b] (8)
Extent of disease (number of bone lesions), *N* (%)		
2–4	4 (12)	0
5–9	7 (21)	3 (23)
10–20	9 (27)	4 (31)
>20	13 (39)	6 (46)
Time since initial diagnosis, median (range), months	73 (7–292)	45 (12–274)
Time since bone metastases, median (range), months	23 (1–58)	10 (0–92)
Prior anticancer therapies, *N* (%)		
Hormonal therapies		
Abiraterone + prednisone	25 (76)	8 (62)
Enzalutamide	3 (9)	5 (38)
Chemotherapy		
Docetaxel	2 (6)	0
Immunostimulants		
Sipuleucel-T	6 (18)	4 (31)
Bone-modifying agents, *N* (%)		
Bisphosphonates	13 (39)	5 (38)
Denosumab	12 (36)	3 (23)
Other, *N* (%)		
Radiation	24 (73)	9 (69)

ALP, alkaline phosphatase; LDH, lactate dehydrogenase; PSA, prostate-specific antigen; ULN, upper limit of normal.
[a] Adrenal (2 patients), pleura, pancreas.
[b] Adrenal.

patients in the docetaxel arm. There were no TEAEs of thrombocytopenia reported in either arm during the treatment period, and median platelet laboratory values were similar for both treatment groups between baseline and day 8 (Supplementary Fig. 2). There were no grade 5 TEAEs. No fractures were observed.

3.2.4. *Efficacy*

PSA declines of >50% occurred in 61% of patients in the combination arm and 54% of patients in the docetaxel arm (Supplementary Fig. 3A). Plots of PSA level relative to baseline from week 4 to end of treatment show similar profiles for both arms, but PSA suppression was more pronounced with the combination arm (Supplementary Fig. 4A, Supplementary Table 4). A longer time to PSA progression was also observed with the combination arm (Fig. 2A; median, 6.6 vs 4.8 months).

The median PFS was 12.0 months in the combination arm and 9.3 months in the docetaxel arm (Fig. 2D). Twelve-month overall survival rates were similar (89% and 90%, respectively), although the high level of censoring precluded meaningful analysis. Disease progression based on RECIST and PCWG2 criteria is shown in Supplementary Table 5.

Changes in bone marker levels indicated a greater suppression of osteoblastic activity in the combination

Table 2
TEAEs in the phase 2a treatment period (any grade and grade 3 or 4): safety population.

TEAE	Any grade		Grade 3 or 4	
	Radium-223 + docetaxel $N = 33$	Docetaxel $N = 13$	Radium-223 + docetaxel $N = 33$	Docetaxel $N = 13$
Any	33 (100)	13 (100)	16 (48)	8 (62)
Haematological[a]				
Neutropenia	10 (30)	5 (38)	10 (30)	5 (38)
Anaemia	3 (9)	1 (8)	1 (3)	0
Leucopenia	2 (6)	2 (15)	2 (6)	2 (15)
Lymphopenia	1 (3)	0	1 (3)	0
Febrile neutropenia	0	2 (15)	0	2 (15)
Non-haematological[b]				
Fatigue	17 (52)	9 (69)	0	0
Nausea	16 (48)	8 (62)	0	0
Diarrhoea	15 (45)	5 (38)	1 (3)	0
Back pain	13 (39)	4 (31)	2 (6)	0
Alopecia	12 (36)	7 (54)	0	0
Peripheral oedema	12 (36)	5 (38)	0	1 (8)
Constipation	11 (33)	5 (38)	0	0
Decreased appetite	11 (33)	4 (31)	0	0
Peripheral neuropathy	10 (30)	4 (31)	0	0
Dysgeusia	7 (21)	8 (62)	0	0
Arthralgia	7 (21)	6 (46)	0	0
Dyspnoea	2 (6)	5 (38)	0	0
Gastrointestinal reflux disease	1 (3)	4 (31)	0	0

TEAEs, treatment-emergent adverse events.
Data are number of patients (%).
[a] Selected because of their relevance to radium-223 and chemotherapy.
[b] Any grade occurring in ≥25% of patients in either treatment group.

arm (Supplementary Fig. 3B, 3C, 4B, C, Supplementary Table 4). For both tALP and bALP, a longer median time to progression was observed for combination arm patients than docetaxel arm patients (9.0 vs 6.9 and 9.3 vs 7.4 months, respectively; Fig. 2B and C).

P1NP showed a decline pattern favouring the combination similar to that for bALP (Supplementary Fig. 3D, 4D). The weighted median area under the time–activity curve for P1NP was substantially smaller for the combination arm (25.0 *v* 46.2 μg*day/L), reflecting greater suppression of this marker (Supplementary Table 6).

Markers of osteoclastic activity, uCTX-1 and ICTP, showed similar patterns of decrease during treatment for combination arm and docetaxel arm patients (Supplementary Fig. 3E, 3F, Fig. 4E, F, Supplementary Table 6).

An antitumour treatment effect in both arms was suggested by the decrease in CTCs (Supplementary Table 7).

4. Discussion

To our knowledge, this trial is the first to explore the concept of dual targeting of osteoblastic bone and cancer cells using two concurrent agents, radium-223 and docetaxel, both of which prolong survival in patients with mCRPC. The concept of targeting bone and tumour is not novel. Prior studies have examined docetaxel in combination with bone-targeting agents that are not known to prolong survival, namely, strontium-89 and rhenium-188-hydroxyethylidine diphosphonate [14,15]. These studies only used one or two doses of the bone-seeking radiopharmaceutical, rather than as a repetitively dosed regimen integrated with chemotherapy. Neither of these studies yielded data sufficiently promising to warrant advancement to phase 3. This study, however, used only life-prolonging agents in a regimen in which patients were exposed to both agents throughout the treatment. Although the combination arm used the step-down dose of docetaxel commonly applied in clinical practice, the cumulative exposure to docetaxel in the two arms of the phase 2a cohort was similar, and the combination was associated with less neutropenia, fatigue, and certain gastrointestinal toxicities. Another factor that may have contributed to the safety profile of the combination is that we administered five doses of radium q6w, rather than six doses every four weeks. Combination therapy appeared to increase the proportion of patients with substantial

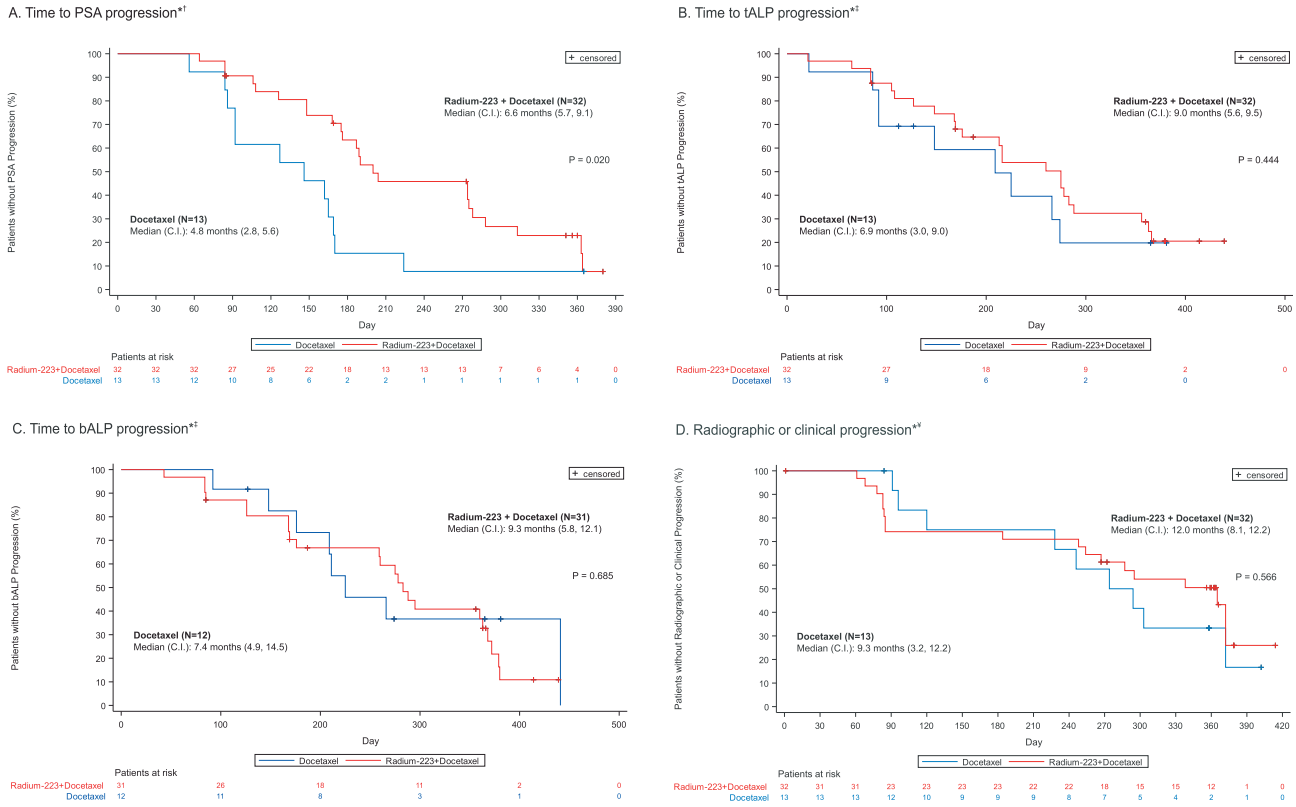


Fig. 2. Kaplan–Meier plots for (A) time to PSA progression; (B) time to tALP progression; (C) time to bALP progression and (D) radiographic or clinical progression-free survival. *Per protocol population; intent-to-treat patients who received ≥40% of specified number of radium-223 injections or docetaxel, per dose escalation study results, and have no major protocol violations. †As per Prostate Cancer Working Group 2 (PCWG2). PSA progression for patients with an initial PSA decline from baseline is defined as a PSA increase ≥25% and ≥2 ng/mL above nadir, confirmed ≥3 weeks later; for those with no PSA decline from baseline, progression is defined as a PSA increase ≥25% and ≥2 ng/mL above baseline after 12 weeks. ‡tALP/bALP progression for patients with an initial decline in tALP/bALP from baseline was defined as a tALP/bALP increase ≥25% above the nadir, confirmed ≥3 weeks later; for patients with no tALP/bALP decline from baseline, progression was defined as a tALP/bALP increase ≥25% above the baseline after 12 weeks. ¥Time to radiographic or clinical progression is a composite end-point encompassing time to first radiographic or clinical progression or death. bALP, bone alkaline phosphatase; CI, confidence interval; PSA, prostate-specific antigen; tALP, total alkaline phosphatase.

declines in levels of PSA and bone formation biomarkers relative to docetaxel alone and appeared to delay time to progression of these markers.

The safety of this combination is increasingly clinically relevant. Patients generally receive abiraterone or enzalutamide as first-line therapy for mCRPC, with chemotherapy reserved for second-line or beyond. After abiraterone or after enzalutamide therapy, patients frequently manifest both bony disease and soft tissue disease [16,17] and remain sensitive to chemotherapy despite the presence of molecular changes that may render tumours resistant to further androgen receptor (AR)–directed therapy [18]. We therefore have an increasing clinical need for a regimen that is non-AR directed and delivers potent therapy both systemically to the cancer cells and also to the osteoblasts surrounding metastatic bone lesions. Radium-223 and docetaxel appear to fulfil these criteria well. This trial suggests that such an approach is safe, with patients followed up for 1 year without the emergence of long-term safety concerns. It is unknown whether the combination prolongs overall survival compared with radium-223 or docetaxel alone, thus warranting further investigation.

5. Conclusions

This study showed that radium-223 (55 kBq/kg q6w) plus docetaxel (60 mg/m^2 q3w) was well tolerated and presented no greater safety concerns than docetaxel alone (75 mg/m^2 q3w). Exploratory efficacy data suggested enhanced antitumour activity in the combination arm. Based on these results, the radium-223/docetaxel combination will be further explored in a phase 3 trial in patients with bone metastatic CRPC (NCT03574571).

Role of the funding source

The study was designed by the funder in conjunction with the coordinating investigator (M.J.M.). The funder collected, analysed and interpreted the study data in collaboration with the authors and commissioned

medical writing support for the drafting of the report. M.J.M. had the final responsibility for the decision to submit for publication.

Conflict of interest statement

M.J.M. discloses consultancy/advisory roles with Astellas Pharma, Bayer, Endocyte and Advanced Accelerator Applications and has received travel/accommodation expenses from Bayer and Endocyte, and his institution has received research funding from Bayer, Endocyte, Progenics and Sanofi; Y.L. discloses consultancy/advisory roles with Astellas Pharma, AstraZeneca, Janssen, Merck Sharp & Dohme, Pfizer, Roche, Seattle Genetics and Sanofi, and his institution has received research funding from Sanofi; C.J.S. declares stock ownership in relation to Leuchemix, consultancy/advisory roles with Astellas Pharma, AstraZeneca, Bayer, Genentech/Roche, Janssen Biotech, Pfizer and Sanofi and intellectual property interests in relation to Leuchemix and Exelixis, and his institution has received research funding from Astellas Pharma, Bayer, Janssen Biotech, Sanofi and Sotio; K.F. has received honoraria from Bayer and Sanofi, discloses consultancy/advisory roles with Amgen, Astellas Pharma, Bayer, Janssen and Sanofi and has received travel/accommodation expenses from Amgen; C.J.R. has received honoraria from Astellas Pharma, Bayer and Janssen Oncology, discloses consultancy/advisory roles with Bayer, Ferring and Millennium and has received research funding from BIND Biosciences, Karyopharm Therapeutics and Novartis; D.H.S. declares participation in speakers' bureau for Bayer; E.S.A. has received honoraria from Astellas Pharma, AstraZeneca, Clovis Oncology, Dendreon, ESSA, Janssen Biotech, Medivation, Merck and Sanofi, discloses consultancy/advisory roles with Astellas Pharma, AstraZeneca, Clovis Oncology, Dendreon, ESSA, Janssen Biotech, Medivation, Merck and Sanofi, has an intellectual property interest in relation to Qiagen and has received travel/accommodation expenses from Dendreon, Medivation and Sanofi, and his institution has received research funding from Aragon Pharmaceuticals, Astellas Pharma, AstraZeneca, Clovis Oncology, Constellation Pharmaceuticals, Dendreon, Exelixis, Genentech, Janssen Biotech, Johnson & Johnson, Merck, Millennium, Novartis, Sanofi and Tokai Pharmaceuticals; N.P-.T. has nothing to disclose; D.D. has received travel/accommodation expenses from Bayer Healthcare and General Electric, and her institution has received research funding from Bayer Healthcare; H.A.J. has received honoraria from Astellas Pharma, Bayer Healthcare and Ipsen and has an intellectual property interest in relation to Cambridge University Press, and her institution has received research funding from GTx and Siemens Healthineers; H.V. discloses a consultancy role with MIM Software, outside the submitted work; O.P. is an employee of Bayer; C.L. is an employee of Bayer and owns company stock; J.A.C. discloses a consultancy/advisory role with Y-mAbs Therapeutics and Bayer and research support from Genentech, Regeneron, Gilead Pharmaceutical and Morphotek; C.S.H. has received honoraria from Genentech, discloses consultancy/advisory roles with Asana BioSciences, Astellas Pharma, Bayer, Blue Earth Diagnostics, Clovis Oncology, Dendreon, Endocyte, Ferring, Myriad Genetics, Orion Corporation and Tolmar Pharmaceuticals, has received travel/accommodation expenses from Asana Biosciences, Astellas Pharma, Bayer, Blue Earth Diagnostics, Clovis Oncology, Dendreon, Endocyte, Ferring, Genentech, Menarini, Orion Pharma GmbH, Myriad Genetics and Pfizer and has an immediate family member who is employed by, has a leadership role in and holds stock in CTI BioPharma, and her institution has received research funding from Aragon Pharmaceuticals, Astellas Pharma, AstraZeneca, Bayer, Dendreon, Emergent BioSolutions, Genentech, Medivation, Pfizer and Roche.

Data availability statement

Availability of the data underlying this publication will be determined according to Bayer's commitment to the EFPIA/PhRMA 'Principles for responsible clinical trial data sharing'. This pertains to scope, time point and process of data access.

As such, on request from qualified scientific and medical researchers, Bayer commits to sharing patient-level clinical trial data, study-level clinical trial data and protocols from clinical trials in patients for medicines and indications approved in the United States (US) and European Union (EU) as necessary for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the EU and US regulatory agencies on or after January 01, 2014.

Interested researchers can use www.clinicalstudydatarequest.com to request access to anonymised patient-level data and supporting documents from clinical studies to conduct further research that can help advance medical science or improve patient care. Information on the Bayer criteria for listing studies and other relevant information is provided in the Study sponsors section of the portal.

Data access will be granted to anonymised patient-level data, protocols and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer will take all necessary measures to ensure that patient privacy is safeguarded.

Acknowledgements

This study was sponsored by Bayer. Medical writing services were provided by Dr. Jim Heighway of Cancer

Communications and Consultancy Ltd, Knutsford, United Kingdom, and were funded by Bayer.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.04.007.

References

[1] Bruland OS, Nilsson S, Fisher DR, Larsen RH. High-linear energy transfer irradiation targeted to skeletal metastases by the alpha-emitter 223Ra: adjuvant or alternative to conventional modalities? Clin Cancer Res 2006;12(20 Pt 2):6250s–7s.

[2] Henriksen G, Fisher DR, Roeske JC, Bruland OS, Larsen RH. Targeting of osseous sites with alpha-emitting 223Ra: comparison with the beta-emitter 89Sr in mice. J Nucl Med 2003;44(2):252–9.

[3] Suominen MI, Fagerlund KM, Rissanen JP, Konkol YM, Morko JP, Peng Z, et al. Radium-223 inhibits osseous prostate cancer growth by dual targeting of cancer cells and bone microenvironment in mouse models. Clin Cancer Res 2017;23(15):4335–46.

[4] Suominen MI, Rissanen JP, Kakonen R, Fagerlund KM, Alhoniemi E, Mumberg D, et al. Survival benefit with radium-223 dichloride in a mouse model of breast cancer bone metastasis. J Natl Cancer Inst 2013;105(12):908–16.

[5] Parker C, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, Fossa SD, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med 2013;369(3):213–23.

[6] Balcer-Kubiczek EK, Attarpour M, Jiang J, Kennedy AS, Suntharalingam M. Cytotoxicity of docetaxel (Taxotere) used as a single agent and in combination with radiation in human gastric, cervical and pancreatic cancer cells. Chemotherapy 2006;52(5):231–40.

[7] Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004;351(15):1502–12.

[8] Bentzen SM, Harari PM, Bernier J. Exploitable mechanisms for combining drugs with radiation: concepts, achievements and future directions. Nat Clin Pract Oncol 2007;4(3):172–80.

[9] Zimmerman BE, Bergeron DE, Cessna JT, Fitzgerald R, Pibida L. Revision of the NIST standard for (223)Ra: new measurements and review of 2008 data. J Res Natl Inst Stand Technol 2015;120:37–57.

[10] Petrylak DP, Tangen CM, Hussain MH, Lara Jr PN, Jones JA, Taplin ME, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med 2004;351(15):1513–20.

[11] Parker CC, Pascoe S, Chodacki A, O'Sullivan JM, Germa JR, O'Bryan-Tear CG, et al. A randomized, double-blind, dose-finding, multicenter, phase 2 study of radium chloride (Ra 223) in patients with bone metastases and castration-resistant prostate cancer. Eur Urol 2013;63(2):189–97.

[12] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228–47.

[13] Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 2008;26(7):1148–59.

[14] James ND, Pirrie SJ, Pope AM, Barton D, Andronis L, Goranitis I, et al. Clinical outcomes and survival following treatment of metastatic castrate-refractory prostate cancer with docetaxel alone or with strontium-89, zoledronic acid, or both: the TRAPEZE randomized clinical trial. JAMA Oncol 2016;2(4):493–9.

[15] van Dodewaard-de Jong JM, de Klerk JMH, Bloemendal HJ, Oprea-Lager DE, Hoekstra OS, van den Berg HP, et al. A randomised, phase II study of repeated rhenium-188-HEDP combined with docetaxel and prednisone versus docetaxel and prednisone alone in castration-resistant prostate cancer (CRPC) metastatic to bone; the Taxium II trial. Eur J Nucl Med Mol Imaging 2017;44(8):1319–27.

[16] Maughan BL, Xhou XC, Suzman DL, Nadal R, Bassi S, Schweizer MT, et al. Optimal sequencing of docetaxel and abiraterone in men with metastatic castration-resistant prostate cancer. Prostate 2015;75(15):1814–20.

[17] Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014;371(5):424–33.

[18] Antonarakis ES, Lu C, Luber B, Wang H, Chen Y, Nakazawa M, et al. Androgen receptor splice variant 7 and efficacy of taxane chemotherapy in patients with metastatic castration-resistant prostate cancer. JAMA Oncol 2015;1(5):582–91.

Clinical Cancer Research

The Role of Lineage Plasticity in Prostate Cancer Therapy Resistance

Himisha Beltran[1], Andrew Hruszkewycz[2], Howard I. Scher[3], Jeffrey Hildesheim[2], Jennifer Isaacs[2], Evan Y. Yu[4], Kathleen Kelly[2], Daniel Lin[4], Adam Dicker[5], Julia Arnold[2], Toby Hecht[2], Max Wicha[6], Rosalie Sears[7], David Rowley[8], Richard White[3], James L. Gulley[2], John Lee[4], Maria Diaz Meco[9], Eric J. Small[10], Michael Shen[11], Karen Knudsen[5], David W. Goodrich[12], Tamara Lotan[13], Amina Zoubeidi[14], Charles L. Sawyers[3], Charles M. Rudin[3], Massimo Loda[15], Timothy Thompson[16], Mark A. Rubin[17], Abdul Tawab-Amiri[2], William Dahut[2], and Peter S. Nelson[4]

Abstract

Lineage plasticity has emerged as an important mechanism of treatment resistance in prostate cancer. Treatment-refractory prostate cancers are increasingly associated with loss of luminal prostate markers, and in many cases induction of developmental programs, stem cell–like phenotypes, and neuroendocrine/neuronal features. Clinically, lineage plasticity may manifest as low PSA progression, resistance to androgen receptor (AR) pathway inhibitors, and sometimes small cell/neuroendocrine pathologic features observed on metastatic biopsy. This mechanism is not restricted to prostate cancer as other malignancies also demonstrate lineage plasticity during resistance to targeted therapies. At present, there is no established therapeutic approach for patients with advanced prostate cancer developing lineage plasticity or small cell neuroendocrine prostate cancer (NEPC) due to knowledge gaps in the underlying biology. Few clinical trials address questions in this space, and the outlook for patients remains poor. To move forward, urgently needed are: (i) a fundamental understanding of how lineage plasticity occurs and how it can best be defined; (ii) the temporal contribution and cooperation of emerging drivers; (iii) preclinical models that recapitulate biology of the disease and the recognized phenotypes; (iv) identification of therapeutic targets; and (v) novel trial designs dedicated to the entity as it is defined. This Perspective represents a consensus arising from the NCI Workshop on Lineage Plasticity and Androgen Receptor-Independent Prostate Cancer. We focus on the critical questions underlying lineage plasticity and AR-independent prostate cancer, outline knowledge and resource gaps, and identify strategies to facilitate future collaborative clinical translational and basic studies in this space.

Introduction

Lineage plasticity is a biological process that occurs during normal development and later as a mechanism that promotes cell survival when adapting to their environment, evading stress, or repairing tissues. Plasticity may manifest as reversible or irreversible changes in cellular "identity," whereby cells take on an alternative morphologic, phenotypic, or epigenetic state (1). In cancer, lineage plasticity facilitates carcinogenesis, metastasis, and treatment resistance (2). During therapy-related lineage plasticity, differentiated tumor cells acquire new phenotypes, in some cases reverting back to a more "stem-like" state followed by redifferentiating toward an alternative "cell fate" in order to bypass therapeutic pressure. This versatility of cellular state is particularly prominent in cancer types with effective therapies that target major growth programs and lineage-directing factors (e.g., BRAF-mutant melanoma, EGFR-mutant lung cancer, AR-driven prostate cancer). In these cases, early "targetable" genomic alterations are often retained, but expression of the pressured target is suppressed. Despite preserving a molecular memory of their differentiated cancer cell precursor, alternative lineage programs facilitate subsequent tumor progression.

Prostate cancer is a malignancy driven by androgen receptor (AR) signaling, and AR-targeted therapies are commonly used to treat patients at all stages of the disease. Prostate tumors most frequently

[1]Dana Farber Cancer Institute, Boston, Massachusetts. [2]National Cancer Institute, Bethesda, Maryland. [3]Memorial Sloan Kettering, New York, New York. [4]University of Washington, Fred Hutchinson Cancer Center, Seattle, Washington. [5]Thomas Jefferson University, Philadelphia, Pennsylvania. [6]University of Michigan, Ann Arbor, Michigan. [7]Oregon Health and Science University, Portland, Oregon. [8]Baylor College of Medicine, Houston, Texas. [9]Sanford Burnham, La Jolla, California. [10]University of California San Francisco, San Francisco, California. [11]Columbia University Irving Medical Center, New York, New York. [12]Roswell Park Cancer Center, Buffalo, New York. [13]Johns Hopkins University, Baltimore, Maryland. [14]University of British Columbia, Vancouver, British Columbia, Canada. [15]Weill Cornell Medicine, New York, New York. [16]MD Anderson, Houston, Texas. [17]University of Bern, Bern, Switzerland.

Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

Corresponding Author: Himisha Beltran, Dana Farber Cancer Institute, 450 Brookline Avenue, Boston, MA 02215. Phone: 617-582-9421; E-mail: himisha_beltran@dfci.harvard.edu

Clin Cancer Res 2019;XX:XX–XX

doi: 10.1158/1078-0432.CCR-19-1423

Translational Relevance

Lineage plasticity associated with loss of androgen receptor signaling dependence and the acquisition of alternative lineage programs occurs in up to 20% of advanced prostate cancer patients as a mechanism of treatment resistance, with important clinical and therapeutic implications. We discuss our current understanding of mechanisms underlying this process and outline a path toward the development of novel biomarkers and trials for this molecularly distinct subset of patients.

display an adenocarcinoma morphology reminiscent of normal luminal prostate architecture, with higher levels of disorganization associated with advanced tumor grade. Downstream markers of canonical AR activity, such as PSA, are used as clinical biomarkers to confirm a diagnosis of prostate cancer and for disease monitoring. Although several prostate cancer drugs are effective at lowering androgen levels and/or blocking the AR directly, metastatic prostate cancers universally develop treatment resistance (3). Acquired resistance is typically due to reactivation of AR signaling mediated, in part, by genomic mutation, amplification, or structural rearrangement of the *AR* gene itself. However, loss of AR expression and/or downstream signaling occurs in an estimated 15% to 20% of castration-resistant tumors (4–6). In extreme cases, tumors may reprogram toward alternative pathways adopting features of neuroendocrine, neuronal, or other lineages. Clinically, these cancers are notable for attenuated AR signaling and a range of histologies of which the most common exhibit small cell neuroendocrine carcinoma characteristics. At present, the definition and mechanistic underpinnings of this subset remain ill-defined, and there are no established therapeutic approaches for small cell/NEPC or other phenotypes. Few clinical trials address lineage plasticity, and the outlook for patients remains poor.

To address the challenges resulting from lineage plasticity, the NCI organized a Workshop focused on Lineage Plasticity and Androgen Receptor-Independent Prostate Cancer. Five working groups were assembled prior to the workshop to formulate questions underlying basic, translational, and clinical knowledge gaps and to develop approaches to address them (Supplementary Information). This Perspective generated as a result of the workshop summarizes concepts, data, deficiencies, and opportunities that drive critical questions underlying lineage plasticity and AR-independent prostate cancer.

Gap 1: A Fundamental Understanding of How Lineage Plasticity Occurs

Lineage plasticity is a term that implies that cells are capable of reprogramming their identity by acquiring an alternative lineage state and that this process is at some point plastic, or reversible. Whether AR-independent treatment resistance is mediated through an intermediate stem-like state, an "epithelial–mesenchymal transition" (EMT), or through direct transdifferentiation to acquire new characteristics and the extent of the reversibility of these processes are not well understood. Tumors with mixed or overlapping features expressing both AR and AR pathway genes as well as neuroendocrine markers ("hybrid" or "amphicrine" tumors), or those lacking both AR and neuroendocrine markers ("double negative" tumors) may further represent distinct disease states or a continuum (Fig. 1). Lineage programs such as gastrointestinal, squamous, and others have also been described (7). Identifying subsets within AR-independent disease provides expanding insights into the unique biology of AR-independent therapy resistance as well as potentially distinct therapeutics, such as the preferential activation of fibroblast growth factor signaling in "double negative" castration-resistant prostate cancer (CRPC; ref. 4).

The transition of prostate cancer away from a luminal epithelial phenotype is facilitated by genomic loss of the tumor suppressors *RB1* and *TP53*, leading to changes in stem cell, developmental, and EMT programs, mediated in part by the lineage pluripotency transcription factor SOX2 (8–10). Downregulation of REST (a transcription factor that normally silences the expression of neuron-specific genes in nonneuronal cells) through splicing

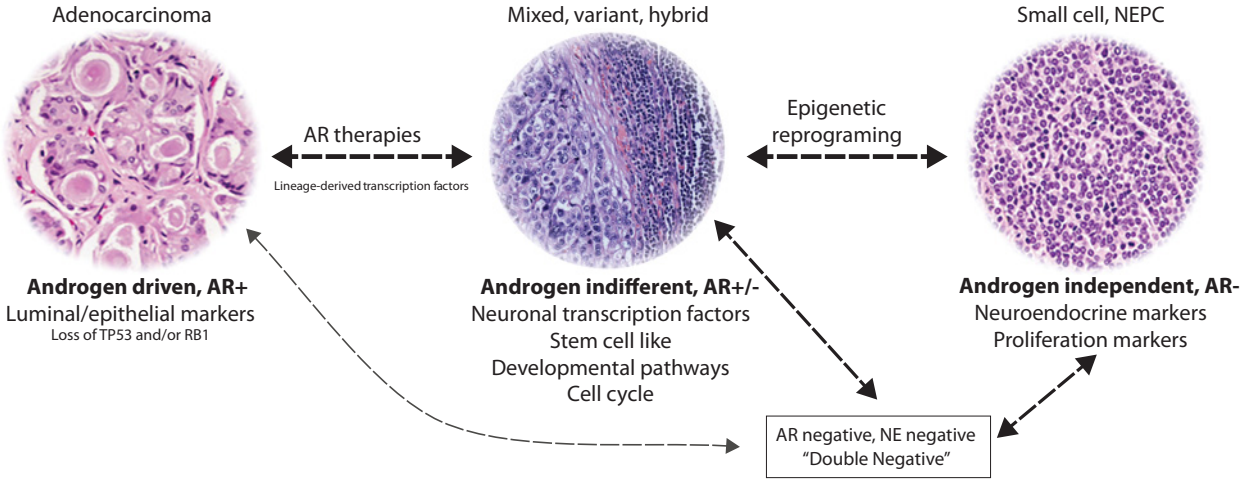


Figure 1.
Schematic of the proposed molecular events and transition states underlying lineage plasticity that occurs during CRPC progression from an AR-positive, AR-driven prostate adenocarcinoma (luminal phenotype) toward an AR-negative, AR-independent cellular state (e.g., small cell/neuroendocrine).

regulated by SRRM4 (11, 12), as well as activation of lineage-associated transcription factors such as N-myc (13, 14), Onecut2 (15, 16), and BRN2 (17), and derepression of developmental genes such as PEG10 (18) also occur. These changes in cellular programs associate with an increase in cellular proliferation and amplification or overexpression of cell-cycle regulators (e.g., aurora kinase, polo-like kinase; refs. 13, 19), leading to aggressive tumor growth and often visceral metastatic spread. Lineage tracing studies (20) have supported a luminal cell of origin of neuroendocrine prostate cancer cells that arise upon potent androgen blockade, supporting a "transdifferentiation" process. Important questions concerning the timing, cooperation, and feedback of the drivers of transdifferentiation processes and their relationships to oncogenic programs and AR silencing remain to be addressed. Further, identification of noncanonical AR programs associated with AR-positive, PSA low tumors as well as genes derepressed by AR inhibition could provide biological insights into other potential early mediators of lineage plasticity. Epigenetic modifications including changes in DNA methylation and upregulation of the polycomb complex gene enhancer of zeste 2 (EZH2) also play a role in silencing the luminal program and in reprogramming lineage (8, 10). Targeting epigenetic programs may result in some degree of reversibility or reversion back to a more luminal state. Metabolic shifts mediated in part by loss of PKCλ/ι (21), which support proliferation and epigenetic changes, as well as changes in tumor hypoxic state (15) are also observed during NEPC progression. A better understanding of the fundamental cellular and molecular interactions that drive lineage plasticity and the role of the tumor microenvironment, metabolic alterations, and changes in epigenetic state requires further focus and study. This will help to further refine the working definition of this cellular state in prostate cancer.

Working definition of lineage plasticity in prostate cancer

A progressive state of CRPC associated with the loss of AR-regulated lineage characteristics and in some situations the acquisition of new phenotypes (e.g., neuroendocrine features). Plasticity is driven by intrinsic and/or acquired alterations in the biological activities of tumor cells and the tumor microenvironment that involve metabolic, genetic, and epigenetic changes. The consequences of these changes comprise a gene expression profile/phenotype consistent with AR/androgen independence and sustained proliferation.

Open questions

- Is loss of canonical AR signaling equivalent to AR independence? For instance, could the presence of AR in cases with low AR signaling still drive a noncanonical program to sustain tumor growth?
- How many lineages are there and how do we best recognize and define them?
- What degree of reversibility underlies lineage plasticity? Could targeting epigenetic alterations completely revert back toward a luminal state, and/or do genetic factors "fix" tumors in an alternate state?
- What are the mechanisms and mediators of tumor microenvironment regulation that underlie lineage plasticity—aging, senescence, inflammation, metabolism, oncogenic, and nononcogenic biological processes; and the cellular dynamics of immune cells, fibroblasts, adipocytes, endothelial, and neuronal cells that effect this process?
- How do lineage determining transcription factors interact or cooperate during prostate cancer progression?
- What extent do factors related to the metastatic environment (e.g., liver, bone) and/or oncogene-associated or therapy-induced senescence contribute to lineage plasticity?

Gap 2: Determining the Temporal Contribution and Cooperation of Emerging Drivers

How AR-directed therapies affect clonal evolution, clonal selection, and the evolutionary bottlenecks that shape lineage plasticity is not well established. Mapping these processes have important clinical implications for biomarkers and therapeutics. For instance, hormone-naïve high-grade localized prostate cancers with low PSA levels may express neuroendocrine genes and harbor lower AR signaling (22), which may represent a high-risk patient population for developing lineage plasticity when later treated with AR pathway inhibitors. *RB1* loss, with or without *TP53* mutation or deletion, also occurs in a subset of prostate adenocarcinomas along the disease spectrum (23, 24), and may identify patients for aggressive surveillance and/or early intervention therapeutic strategies. The timing and cooperation of lineage-derived transcription factors further shape downstream programs as well as the epigenetic landscape. Whether intermittent AR inhibition, potentially alternating with therapies that target these alterations to induce differentiation, could delay the onset of lineage plasticity or prevent its emergence due to reconstitution of the tumor ecosystem with luminal lineage cells is intriguing and requires further study.

Understanding how mixed CRPC tumors that express both AR and neuroendocrine (or other) markers respond to AR therapies, and whether double-negative and small cell NEPC share treatment vulnerabilities such as sensitivity to platinum chemotherapy have important clinical implications for therapy selection. Assessment of the impact of emerging therapies (and combination approaches) on the prevention or reversal of phenotype or for their impact on tumor kill will help refine treatment goals; the readouts from targeting epigenetic alterations or alternative splicing, for instance, may differ from the goals of targeting proliferation or downstream effects of fixed genomic events. Serial metastatic biopsies or liquid biopsies will be useful for understanding the sequence of aberrations in patients and, when combined with clinical features such as PSA trends and sites of radiologic progression, have the potential to improve the diagnosis of patients progressing through the various biological disease states and to help refine clinical endpoints. One proposed translational research strategy for identifying the context and impact of RB1 alterations is highlighted in Box 1.

Open questions

- What are the relationships between lineage drivers and oncogenic programs?
- Does the presence of *RB1* and/or *TP53* aberrations in *prostate adenocarcinoma* predispose patients toward developing lineage plasticity and small cell/neuroendocrine features?
- Is there an intermediate clinical state where intervention may be effective in preventing or reversing lineage plasticity?
- Do PSA dynamics adequately reflect AR signaling in patients?

Box 1. One of the proposed translational research strategies developed at the workshop to address the role and cooperation of *RB1* and *TP53* in driving lineage plasticity in prostate cancer and other Rb1-deficient tumors (e.g., small cell lung cancer, SCLC) and an approach toward the development of novel biomarker-driven therapeutics.

What are the vulnerabilities in NEPC versus SCLC and other RB-deficient cancers?

Aim 1: Develop a series of collaborating institutions with large clinical volumes of CRPC patients and clinical databases to determine clinical parameters associated with RB loss ± TP53 loss and type of alteration (mutation; copy loss). Compare with other dual RB/p53 loss cancer types (SCLC).

Aim 2: Develop tissue and blood-based markers (IHC/ISH/transcriptional/proteomic/metabolic signatures) that detect/identify and associate with specific RB1 ± TP53 aberrations.

Aim 3: Develop isogenic models of RB ±TP53 deficiency in prostate cancer backgrounds [cell lines, patient-derived xenograft (PDX), organoids] to assess: (i) molecular consequence for E2F and TP53 signaling, (ii) biological impact, and (iii) relevance for reflecting clinical observations as per Aim 1.

Aim 4: Utilize models developed in Aim 3 to screen for vulnerabilities/synthetic lethality using high-throughput strategies (e.g., CRISPR screening, FDA-approved compound screening) with the goal of establishing the foundation for the next phase of clinical testing

Aim 5: Refine strategies for accurately assessing RB and TP53 status in liquid biopsy, and develop longitudinal studies to determine the impact on progression from prostate cancer to CRPC to NEPC.

- How and when is the AR lost in the context of disease progression and how do specific therapeutics influence resistance pathways?
- Are there strategies to maintain cell differentiation and AR dependency while still restraining tumor growth?
- Do increased DNA damage response gene activities, or other specific transcriptional signatures contribute to the lineage plasticity program, and can these activities be exploited therapeutically?
- Are there synthetic lethal therapeutic approaches that may be exploited to target lineage plasticity and AR-independent prostate cancer?
- What degree of intratumoral heterogeneity is seen within and across metastases in individual patients?

Gap 3: Preclinical Models That Recapitulate Biology of the Disease and the Recognized Phenotypes

Preclinical models that represent the prostate cancer disease spectrum are essential for understanding biology and for the

Box 2: Glossary

AR signaling (canonical): androgen receptor signaling that occurs through ligand (androgen)-mediated or ligand-independent means, resulting in activation of downstream programs critical for prostate growth, development, and function

AR signaling independent or AR indifferent: sustained growth of prostate tumor cells that is not driven by or reliant on downstream canonical AR signaling

Cellular identity or differentiation: a means of classifying cells based on their phenotype or physiologic function

Cellular determination: the process by which a cell becomes specialized to perform a specific function

Clonality: cells that share a common ancestry

Differentiation: the process by which a stem cell or progenitor cell matures into a cell with a specific identity. Dedifferentiation is when a differentiated cell loses its matured cellular identity to become less mature and more stem-like

Double-negative prostate cancer: a subset of castration-resistant prostate cancer that does not express the AR and also does not express neuroendocrine markers

Epigenome/epigenetics: changes in gene expression and cellular phenotype caused by mechanisms other than changes in DNA

Epithelial–Mesenchymal Transition: a process by which epithelial cells lose their cell–cell adhesion and gain migratory and invasive properties to become more like mesenchymal cells, which may facilitate cancer growth and metastatic spread

Embryonic stem cells: pluripotent stem cells that have the potential to differentiate into multiple cell types and are capable of self-renewal

Lineage determining transcription factors: proteins that bind to DNA, either alone or in cooperation with other partners, to control transcriptional output of a cell type to regulate its phenotype and functional characteristics

Lineage reprogramming: the conversion of a mature, terminally differentiated cell type into another mature cell type with or without undergoing dedifferentiation

Lineage tracing: A method that delineates all progeny produced by a single cell or a group of cells

Multipotent: Potential of a cell to form different lineages

Plasticity: Ability of a cell to convert from one cell type to another. This may refer to the potential of a differentiated cell to dedifferentiate and then redifferentiate into a new state

Progenitor: ancestor cell that gives rise to a specific type of differentiated cell

Neuroendocrine: cells that are neural and endocrine in structure or function. In the pathologic classification of neoplasms, this designation is typically based on tumor morphology rather than function. Well-differentiated neuroendocrine tumors (e.g., carcinoids) and poorly differentiated neoplasms (e.g., small cell carcinoma) have distinct biology and may arise in various anatomic sites

Pluripotent: A cell that is capable of developing into any cell type

Small cell carcinoma: morphologic definition based on pathologic review of tumor hematoxylin and eosin–stained slides demonstrating small blue cells, high-grade features, scant cytoplasm, and distinct nuclear features (i.e., fine chromatin,

lacking prominent nucleoli). Protein expression of classical neuroendocrine markers such as chromogranin or NSE may be present but is not required

Stem-like: cells that possess characteristics similar to normal stem cells, such as the ability to give rise to other cell types within a tumor

Transdifferentiation: reprogramming of a differentiated cell of one lineage into a differentiated cell of another lineage

development of novel therapeutics. Currently, the number and types of cell lines that recapitulate lineage plasticity are limited, though there are PDX and organoid models of AR-negative and neuroendocrine prostate cancer that have been described and characterized (refs. 25–29; Table 1). Dynamic *in vivo* models, such as a PDX model that changes phenotype from an AR-positive adenocarcinoma to an AR-negative NEPC (30), and xenografts that lose AR signaling dependence during enzalutamide resistance (17) have been used to capture the lineage plasticity process. Genetically engineered mouse models such as the TRAMP model and others designed to alter key molecular events, including loss

Table 1. Preclinical models

Model	Source	Pathologic and molecular features
NCI-H660 cell line	Lymph node metastasis	Small cell carcinoma; AR-negative; PSA-negative; TMPRSS2-ERG gene fusion-positive; synaptophysin, CD56, NSE-positive
LuCAP 49, 93, 145.1, 145.2 patient derived xenograft (PDX) and PDX–organoid models	Omental metastasis (LuCAP 49), TURP (LuCAP 93), liver (LuCAP 145.1), lymph node (LuCAP 145.2)	Neuroendocrine histology; AR-negative; synaptophysin-positive
MDA PCa 144-4, 144-13, 155-2, MDA PCa 177-0, MDA PCa 189-1 PDX models	Salvage pelvic exenteration (MDA 144, MDA 155-2), prostate (MDA 177, MDA 189-1)	Small cell and large cell carcinoma; Aggressive variant clinical features; TMPRSS2-ERG gene fusion positive (MDA 144)
LTL352 and LTL370 PDX models	Urethral (LTL352) and penile (LTL370) metastasis	Small cell carcinoma; AR-negative; PSA-negative; synaptophysin, NSE-positive
LTL331 transdifferentiation PDX model	Primary prostate cancer (LTL331) PDX model that develops castration-resistant NEPC *in vivo* (LTL331R)	Primary high-grade adenocarcinoma (LTR331) and neuroendocrine prostate cancer histology (LTL331R); TMPRSS2-ERG fusion-positive; LTR331: AR-positive; LTL331R: AR-negative, PSA-negative, Synaptophysin-positive, chromogranin-positive, CD56-positive
Enzalutamide-resistant LNCaP (42D, 42F)	Cell lines developed from enzalutamide-resistant LNCaP xenograft tumors	AR-positive; PSA low; chromogranin, synaptophysin-positive
MSK-PCA4 Patient-Derived Organoids	Pleural effusion	Neuroendocrine features; AR low; Synaptophysin-positive
WCM Patient-Derived Organoids	Metastatic lesions liver (155), bone (154), lymph node (1,078), soft tissue (1,262)	Small cell carcinoma; AR-negative; PSA-negative; synaptophysin, NSE, chromogranin-positive
TRAMP mouse	C57BL/6 mice expressing the rat probasin driving expression of SV40 large and small T antigens in prostatic epithelial cells	Adenocarcinoma to small cell carcinoma; Rb1 and Tp53 loss; Visceral metastases
$p53^{PE-/-}Rb^{PE-/-}$ mouse	Conditional knockout of p53 and Rb ($p53^{PE-/-}$; $Rb^{PE-/-}$) from the epithelium of all lobes of the mouse prostate	Small cell carcinoma; Rb1 and Tp53 loss
N-Myc-myrAKT1 mouse	Human prostate basal cells overexpressing NMYC and AKT1 implanted subcutaneously in NOD-SCID-IL2Rγnull (NSG) mice	Neuroendocrine features; AR low; chromogranin, synaptophysin-positive
$Pten^{f/f}$;LSL-$MYCN^{+/+}$ mouse	GEMM mice carrying *MYCN* gene integrated into the ROSA26 (*LSL-MYCN*) locus, a Tmprss2-driven tamoxifen-activated Cre recombinase and a *Pten* conditional knockout allele	Divergent differentiation Neuroendocrine features; AR low/AR-negative; chromogranin, synaptophysin-positive; visceral metastases with castration
PBCre4:*Pten*$^{f/f}$:*Rb1*$^{f/f}$ (DKO), PBCre4:Ptenf/f:Rb1f/f:Trp53f/f (TKO)	GEMM mice, PBCre4 transgene is used to delete floxed alleles specifically in prostate epithelium	Neuroendocrine features with metastases; AR-positive/AR low; Synaptophysin-positive
NPp53 mice	GEMM mice, inducible *Nkx3.1*^{CreERT2} driver to delete PTEN and TP53 genes in adult prostate epithelium	Abiraterone-resistant; neuroendocrine features- transdifferentiation (lineage tracing); AR low/AR-negative; Synaptophysin-positive
Ptenf/f-Prkcif/f-PbCre4+ mice (DKO)	GEMM mice, Ptenf/f-PbCre4+ mouse line (PTEN KO) with PTEN specifically deleted in the prostate epithelium, crossed with Prkcif/f mice	Neuroendocrine features; AR low/AR-negative; chromogranin, synaptophysin-positive

NOTE: Table of preclinical models that display lineage plasticity, small cell /NEPC histologic or molecular features, and/or AR-signaling indifference.

of *PTEN*, *TP53*, and *RB1*, and/or gain of *MYCN*, are also useful tools to study the cooperation and timing of emerging tumor suppressors and oncogenes (9, 10, 14, 20, 21, 31). Optimizing and sharing protocols for model development and optimization was discussed as an unmet need, especially as fresh tumor biopsies are more commonly performed clinically and may be used for patient-derived model generation.

Open questions

- What are the preclinical models that can be manipulated in such a way to reflect transition from androgen-dependent to -independent states and further transitions that encompass new differentiation programs such as neuroendocrine phenotypes?
- Are the genomics, transcriptomics, epigenetics, and metabolomics of these model systems representative of advanced human prostate cancer? Do they change over time or with conditions?
- Can we develop a series of paired PDX–organoids with morphologic and molecular information of organoids, PDXs, and human tumor of origin representing the complex molecular landscapes of prostate cancer?
- How do we use model systems to assess reversibility and thereby understand the degree of plasticity?
- What are "the human models" that can be utilized to compare and contrast with the animal models (e.g., rapid autopsies, CTCs, cfDNA, etc.)?

Gaps 4 and 5: Identification of Therapeutic Targets and Novel Trial Designs Dedicated to the Entity as It Is Defined

Given the relatively high reported frequency of small cell NEPC post AR-directed therapy, the National Comprehensive Cancer Network (NCCN) guidelines now recommend consideration of metastatic biopsy for any CRPC patient to look for small cell transformation. If found, patients could be considered for platinum-based chemotherapy based on extrapolation of clinical data for small cell lung cancer and supported by recent platinum-chemotherapy studies in aggressive variant prostate cancer (32). Although these practice guidelines have recently changed, the diagnosis of lineage plasticity remains a clinical challenge due to a lack of standardized or widely accepted clinical or pathologic criteria. Although pure small cell carcinoma defined by morphology is most often congruent between pathologists, those with mixed/hybrid or with varied degrees of neuroendocrine differentiation are often subject to interobserver variability (33).

The diagnosis of other phenotypes may require more detailed studies that involve IHC or other measures of gene expression. There are no standard criteria for when to perform ancillary studies such as IHC for classical neuroendocrine markers (e.g., chromogranin, synaptophysin), AR protein, PSA, or other markers (34, 35). There are also times when AR is expressed in NEPC, but the canonical AR transcriptome (including downstream targets like PSA) is low; identification of downstream genes that may be activated by AR in this setting would be informative and potentially help refine definitions. The incidence of AR-negative or AR-low CRPC without NEPC features or alternative lineage CRPC and the degree of heterogeneity within this spectrum are also not known. The workshop discussed a path toward the standardization of tumor morphology nomenclature and systematic prioritization of ancillary testing in metastatic CRPC (Table 2).

Table 2. Pathology morphology and available ancillary testing

Morphology
%tumor
%glandular
%small cell
Protein studies (**bold** indicates existing CLIA-validated biomarkers)
Molecular/Cell cycle
• **Rb** (Rb function: cyclin D1/p16)
• **P53** (p53 function: p21)
• **Ki-67** (discovery for threshold)
Lineage markers
• **Chg** (Canonical)
• **Syp** (Canonical)
• **CD56**
• **FOXA2**
• **INSM1**
• ASCL
• **Cytokeratin—Cam5.2**
• **Neurofilament**
Androgen signaling
• **AR** (canonical)
• AR-v7
• **PSA**

NOTE: Prioritization of pathology assessment when lineage plasticity is suspected. Tissue should be evaluated for morphologic characteristics that may support small cell carcinoma, neuroendocrine differentiation, or other histologies. Possible ancillary protein studies to consider performing by IHC are listed, with markers in **bold** indicating existing Clinical Laboratory Improvement Amendments (CLIA) grade tests.

Given the current challenges of performing tumor biopsies and the variability in morphologic features that occur after therapy, platinum-based chemotherapy trials have been conducted for patient with aggressive clinical features even in the absence of tumor biopsy (32). Notably, these patients defined by clinical features suggestive of AR independence often harbor combined somatic tumor alterations involving *PTEN*, *TP53*, and/or *RB1*, similar to what has been observed in small cell NEPC (29).

With a loss of AR expression, tumors may also lose other related proteins including prostate-specific membrane antigen (PSMA). This manifests clinically as PSMA-negative lesions on PSMA PET imaging. Low or heterogeneous PSMA PET-CT combined with FDG positivity identifies patients with poor prognosis (36), therefore representing a potential noninvasive means to identify AR-independent resistance. However, there are still many unknowns regarding PSMA regulation and PSMA imaging characteristics along prostate cancer progression and therapy resistance. Multi-institutional collaborative studies combining PSMA with FDG PET imaging, in combination with tumor biopsies of discordant lesions and liquid/tissue molecular assessment, were designed at the workshop.

There is no known effective next-line therapy for patients with small cell NEPC especially after platinum chemotherapy. Although second-line SCLC regimens may be considered, their data in prostate cancer are scarce. Notably, although loss of AR activity eliminates the AR pathway as a therapeutic target, the acquisition of new characteristics that associate with NEPC and other phenotypes exposes new targets and vulnerabilities. Available drugs targeting the AURKA/MYCN or AURK/RB1 axis, LSD1,

EZH2, DLL3, and approaches to target the immune landscape (e.g., vaccine, TGFβi, IL8i, and immune checkpoint inhibitors) are in development for NEPC, as well as drugs targeting FGF/MAPK for double-negative CRPC. The design of rational combination or cotargeting strategies, such as EZH2 inhibition in combination with AR pathway inhibitors or immunotherapy, may also have value. Ultimately, defining the appropriate inclusion criteria and endpoints for trials focused on lineage plasticity will be critical. Trials will require multicenter collaboration and molecularly based biomarker inclusion and careful patient selection. Incorporation of emerging molecular biomarkers in combination with clinical features may help distinguish subcategories of AR-independent CRPC and inform the development of liquid and imaging biomarker approaches for clinical trial design.

Open questions

- What are the clinical and pathologic differences between small cell carcinoma and CRPC with neuroendocrine differentiation? Are IHC markers required and do they capture AR activity?
- Is the increased detection of small cell/NEPC due to increased awareness or is this due to more potent AR-directed therapies? Will the incidence of NEPC increase with recent approvals of potent AR-targeted drugs earlier in the disease (i.e., metastatic castrate-sensitive prostate cancer and nonmetastatic castration-resistant prostate cancer)?
- How well does loss of PSMA or PSMA heterogeneity on imaging in combination with FDG PET-CT noninvasively identify patients developing lineage plasticity? What other radiologic or radiomic (i.e., subvisual tools) may be applied for the early detection of lineage plasticity?
- Platinum sensitivity is also mediated by germline or somatic alterations involving DNA repair genes, which occurs in approximately 20% of CRPC independent of histology. What is the degree of overlap between DNA repair deficiency and lineage plasticity?
- Is reversal of phenotype or tumor kill the primary goal of therapy? What clinical endpoints may be used to assess these outcomes?
- What would a multiarm clinical trial design look like for patients developing lineage plasticity and AR-independent prostate cancer? Which clinical or molecular features are ready to use as inclusion criteria?

Lessons from Other Cancer Types (the Scope of the Problem)

Similar to prostate cancer, malignancies arising from other anatomic sites, tissues, and cell types also develop lineage plasticity as a mechanism of therapy resistance. For instance, 5% to 15% of *EGFR*-mutant lung adenocarcinomas transform to SCLC histology during acquired resistance to EGFR-targeted therapies with retention of the original *EGFR* mutation (37). Cases of small cell transformation in lung cancer have also been reported after immunotherapy (38). *RB1* and *TP53* genomic alterations are universally present in both *de novo* and transformed SCLC and rarely present in unselected lung adenocarcinomas other than those that later develop histologic transdifferentiation (39–41). Whether preexisting *RB1* and *TP53* loss may be used as biomarkers to identify high-risk lung adenocarcinoma patients for alternative treatments is yet to be determined. Understanding whether this predisposition for lineage plasticity is also the case for the subset of castration-resistant prostate adenocarcinomas and localized prostate cancers that harbor *TP53*/*RB1* loss has important implications for the early detection and management. In melanoma, phenotypic switching with distinct cellular populations (e.g., invasive vs. proliferative) and developmental cell states (i.e., MITF low or high) frequently coexisting and dynamically regulated plays a central role in metastasis and therapy resistance (42–44). This switching is hypothesized to be largely regulated by epigenetic modifiers, hypoxia, and the tumor microenvironment, but specific factors remain to be fully elucidated. Similar to prostate cancer, much is still to be learned in melanoma plasticity regarding the number and types of phenotypic states that coexist and their interface with the genetics of the tumor (i.e., do some genomic lesions make the cells more or less responsive to plasticity signals?). In pancreatic ductal adenocarcinoma, lineage heterogeneity associates with poor outcomes; lineage tracing studies have pointed to an acinar cell of origin of neuroendocrine cells, and this is regulated by MYC and epigenomic changes in response to environmental signals (45). A subset of breast cancers also develop lineage plasticity, and in some cases, the luminal phenotype and/or estrogen receptor expression are lost with disease progression; this process may be mediated in part by subpopulations of cells with stem-like properties (46). Given these disease parallels, emerging mechanisms underlying plasticity, stemness, and cellular reprogramming during therapy resistance are pointing to shared mechanisms and potential targets across malignancies.

Summary

It is increasingly recognized that a subset of prostate cancers evades AR-targeted therapies through the development of lineage plasticity. This is associated with loss of AR or AR signaling, frequent *RB1*/*TP53* loss of function, and activation of alternative lineage programs including neuronal, neuroendocrine, stem-like, and developmental pathways. In some instances, lineage plasticity occurs directly through transdifferentiation processes, whereas in other situations, tumor cells dedifferentiate to a stem-like state followed by reprogramming to a new phenotype. Continued tumor evolution under treatment pressures may occur through clonal selection. Although there are many open questions, recent studies have identified newly relevant biological pathways and actionable targets. Addressing the outlined gaps in knowledge will ultimately accelerate the translation of new biologic discoveries into the clinic.

Disclosure of Potential Conflicts of Interest

H. Beltran is a consultant/advisory board member for Janssen, Sanofi Genzyme, and Astellas. H.I. Scher is a consultant/advisory board member for Amgen and Janssen. E.Y. Yu is a consultant/advisory board member for Amgen, Dendreon, Bayer, Merck, AstraZeneca, QED, Incyte, Tolmar, EMD Serono, Pharmacyclics, Seattle Genetics, and Janssen. A. Dicker holds ownership interest (including patents) in Oncohost, is a consultant/advisory board member for Roche, Oncohost, Google, Dreamit Ventures, EMD Serono, Janssen, Cybrexa, and Self Care Catalysts, and reports receiving other remuneration from Wilson Soncini. R. White is a consultant/advisory board member for N-of-One, Inc. E.J. Small holds ownership interest (including patents) in Fortis Therapeutics and Harpoon Therapeutics, and is a consultant/advisory board member for Janssen, Fortis Therapeutics, Tolero Pharmaceuticals, and Beigene Therapeutics. T. Lotan

reports receiving other commercial research support from GenomeDx and Roche, and is a consultant/advisory board member for Janssen. C.L. Sawyers holds ownership interest (including patents) in Novartis, Enzalutamide, and Apalutamide, and is a consultant/advisory board member for Novartis, Agios, Beigene, Blueprint, Column Group, Nextech, Housey Pharma, Foghorn, KSQ, PMV, ORIC, and Petra. C.M. Rudin reports receiving commercial research grants from Daiichi Sankyo, and is a consultant/advisory board member for AbbVie, Amgen, Ascentage, Astra Zeneca, Bristol-Myers Squibb, Celgene, Daiichi Sankyo, Genentech/Roche, Ipsen, Loxo, Pharmamar, Vavotek, Bridge Medicines, and Harpoon Therapeutics. M.A. Rubin reports receiving commercial research grants from Janssen and Eli Lilly, speakers bureau honoraria from Roche and Novartis, and holds ownership interest (including patents) in in the field of NEPC. P.S. Nelson is a consultant/advisory board member for Janssen, Astellas, and Roche. No potential conflicts of interest were disclosed by the other authors.

Supplementary Information

Pre-meeting document with Working Group summaries and questions

Authors' Contributions

Conception and design: H. Beltran, A. Hruszkewycz, H.I. Scher, J. Hildesheim, J. Isaacs, E.Y. Yu, M. Diaz Meco, E.J. Small, K. Knudsen, D.W. Goodrich, T. Lotan, M. Loda, T. Thompson, M.A. Rubin, W. Dahut, P.S. Nelson
Development of methodology: H. Beltran, H.I. Scher, A. Dicker, T. Thompson, M.A. Rubin
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A. Dicker, T. Thompson, M.A. Rubin
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): H. Beltran, H.I. Scher, E.Y. Yu, M. Wicha, M. Diaz Meco, C.M. Rudin, W. Dahut
Writing, review, and/or revision of the manuscript: H. Beltran, A. Hruszkewycz, H.I. Scher, J. Hildesheim, E.Y. Yu, K. Kelly, D. Lin, A. Dicker, J. Arnold, T. Hecht, M. Wicha, D. Rowley, R. White, J.L. Gulley, J. Lee, M. Diaz Meco, E.J. Small, M. Shen, K. Knudsen, D.W. Goodrich, T. Lotan, A. Zoubeidi, C.L. Sawyers, C.M. Rudin, M. Loda, T. Thompson, M.A. Rubin, A. Tawab-Amiri, W. Dahut, P.S. Nelson
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A. Hruszkewycz, H.I. Scher, J. Arnold, D. Rowley, M.A. Rubin, P.S. Nelson, H. Beltran
Study supervision: H. Beltran, T. Thompson
Other (Spearheaded the workshop that led to this manuscript. Co-organized and contributed to the selection of experts participating to the workshop): A. Hruszkewycz
Other (Part of a team of NCI Program Directors and NCI-funded researchers that helped develop and structure the workshop): J. Hildesheim
Other (Discussion with the other authors): T. Hecht
Other (collaborative scientific input): R. Sears

Acknowledgments

This article represents a consensus perspective arising from the NCI Workshop on Lineage Plasticity and Androgen Receptor-Independent Prostate Cancer (held December 2018), a joint effort by the NCI's Division of Cancer Treatment and Diagnosis, Division of Cancer Biology, Center for Cancer Research, and Coordinating Center for Clinical Trials together with investigators of the NCI SPOREs in Prostate Cancer and the Prostate Cancer Task Force of the NCI Genitourinary Steering Committee. It was cochaired by H. Beltran, W. Dahut, and P.S. Nelson. The goal was to assemble leaders in the field to share scientific insights and identify emerging opportunities in basic, translational, and clinical research. We thank Tamara Walton with her help in the planning and coordination of the workshop. This perspective is dedicated to Dr. Andrew Hruszkewycz, recently deceased, whose scientific expertise, dedication, and genuine passion were instrumental in the success of this workshop.

Received May 7, 2019; revised June 7, 2019; accepted July 25, 2019; published first July 30, 2019.

References

1. Graf T, Enver T. Forcing cells to change lineages. Nature 2009;462:587–94.
2. Meacham CE, Morrison SJ. Tumour heterogeneity and cancer cell plasticity. Nature 2013;501:328–37.
3. Watson PA, Arora VK, Sawyers CL. Emerging mechanisms of resistance to androgen receptor inhibitors in prostate cancer. Nat Rev Cancer 2015;15:701–11.
4. Bluemn EG, Coleman IM, Lucas JM, Coleman RT, Hernandez-Lopez S, Tharakan R, et al. Androgen receptor pathway-independent prostate cancer is sustained through FGF signaling. Cancer Cell 2017;32:474–89.e6.
5. Aggarwal R, Huang J, Alumkal JJ, Zhang L, Feng FY, Thomas GV, et al. Clinical and genomic characterization of treatment-emergent small-cell neuroendocrine prostate cancer: a multi-institutional prospective study. J Clin Oncol 2018;36:2492–503.
6. Abida W, Cyrta J, Heller G, Prandi D, Armenia J, Coleman I, et al. Genomic correlates of clinical outcome in advanced prostate cancer. Proc Natl Acad Sci U S A 2019;116:11428–36.
7. Shukla S, Cyrta J, Murphy DA, Walczak EG, Ran L, Agrawal P, et al. Aberrant activation of a gastrointestinal transcriptional circuit in prostate cancer mediates castration resistance. Cancer Cell 2017;32:792–806.e7.
8. Beltran H, Prandi D, Mosquera JM, Benelli M, Puca L, Cyrta J, et al. Divergent clonal evolution of castration-resistant neuroendocrine prostate cancer. Nat Med 2016;22:298–305.
9. Mu P, Zhang Z, Benelli M, Karthaus WR, Hoover E, Chen CC, et al. SOX2 promotes lineage plasticity and antiandrogen resistance in TP53- and RB1-deficient prostate cancer. Science 2017;355:84–8.
10. Ku SY, Rosario S, Wang Y, Mu P, Seshadri M, Goodrich ZW, et al. Rb1 and Trp53 cooperate to suppress prostate cancer lineage plasticity, metastasis, and antiandrogen resistance. Science 2017;355:78–83.
11. Lapuk AV, Wu C, Wyatt AW, McPherson A, McConeghy BJ, Brahmbhatt S, et al. From sequence to molecular pathology, and a mechanism driving the neuroendocrine phenotype in prostate cancer. J Pathol 2012;227:286–97.
12. Zhang X, Coleman IM, Brown LG, True LD, Kollath L, Lucas JM, et al. SRRM4 expression and the loss of REST activity may promote the emergence of the neuroendocrine phenotype in castration-resistant prostate cancer. Clin Cancer Res 2015;21:4698–708.
13. Beltran H, Rickman DS, Park K, Chae SS, Sboner A, MacDonald TY, et al. Molecular characterization of neuroendocrine prostate cancer and identification of new drug targets. Cancer Discov 2011;1:487–95.
14. Dardenne E, Beltran H, Benelli M, Gayvert K, Berger A, Puca L, et al. N-Myc induces an EZH2-mediated transcriptional program driving neuroendocrine prostate cancer. Cancer Cell 2016;30:563–77.
15. Guo H, Ci X, Ahmed M, Hua JT, Soares F, Lin D, et al. ONECUT2 is a driver of neuroendocrine prostate cancer. Nat Commun 2019;10:278.
16. Rotinen M, You S, Yang J, Coetzee SG, Reis-Sobreiro M, Huang WC, et al. ONECUT2 is a targetable master regulator of lethal prostate cancer that suppresses the androgen axis. Nat Med 2018;24:1887–98.
17. Bishop JL, Thaper D, Vahid S, Davies A, Ketola K, Kuruma H, et al. The master neural transcription factor BRN2 is an androgen receptor-suppressed driver of neuroendocrine differentiation in prostate cancer. Cancer Discov 2017;7:54–71.
18. Akamatsu S, Wyatt AW, Lin D, Lysakowski S, Zhang F, Kim S, et al. The placental gene PEG10 promotes progression of neuroendocrine prostate cancer. Cell Rep 2015;12:922–36.
19. Beltran H, Oromendia C, Danila DC, Montgomery B, Hoimes C, Szmulewitz RZ, et al. A phase II trial of the aurora kinase A inhibitor alisertib for patients with castration resistant and neuroendocrine prostate cancer: efficacy and biomarkers. Clin Cancer Res 2019;25:43–51.
20. Zou M, Toivanen R, Mitrofanova A, Floch N, Hayati S, Sun Y, et al. Transdifferentiation as a mechanism of treatment resistance in a mouse model of castration-resistant prostate cancer. Cancer Discov 2017;7:736–49.
21. Reina-Campos M, Linares JF, Duran A, Cordes T, L'Hermitte A, Badur MG, et al. Increased serine and one-carbon pathway metabolism by PKCλ/ι deficiency promotes neuroendocrine prostate cancer. Cancer Cell 2019;35:385–400.e9.

22. Mahal BA, Yang DD, Wang NQ, Alshalalfa M, Davicioni E, Choeurng V, et al. Clinical and genomic characterization of low-prostate-specific antigen, high-grade prostate cancer. Eur Urol 2018;74: 146–54.
23. Robinson D, Van Allen EM, Wu YM, Schultz N, Lonigro RJ, Mosquera JM, et al. Integrative clinical genomics of advanced prostate cancer. Cell 2015; 161:1215–28.
24. Kaur HB, Lu J, Guedes LB, Maldonado L, Reitz L, Barber JR, et al. TP53 missense mutation is associated with increased tumor-infiltrating T-cells in primary prostate Cancer. Hum Pathol 2019;87:95–102.
25. Nguyen HM, Vessella RL, Morrissey C, Brown LG, Coleman IM, Higano CS, et al. LuCaP prostate cancer patient-derived xenografts reflect the molecular heterogeneity of advanced disease an–d serve as models for evaluating cancer therapeutics. Prostate 2017;77:654–71.
26. Gao D, Vela I, Sboner A, Iaquinta PJ, Karthaus WR, Gopalan A, et al. Organoid cultures derived from patients with advanced prostate cancer. Cell 2014;159:176–87.
27. Puca L, Bareja R, Prandi D, Shaw R, Benelli M, Karthaus WR, et al. Patient derived organoids to model rare prostate cancer phenotypes. Nat Commun 2018;9:2404.
28. Beshiri ML, Tice CM, Tran C, Nguyen HM, Sowalsky AG, Agarwal S, et al. A PDX/organoid biobank of advanced prostate cancers captures genomic and phenotypic heterogeneity for disease modeling and therapeutic screening. Clin Cancer Res 2018;24:4332–45.
29. Aparicio AM, Shen L, Tapia EL, Lu JF, Chen HC, Zhang J, et al. Combined tumor suppressor defects characterize clinically defined aggressive variant prostate cancers. Clin Cancer Res 2016;22:1520–30.
30. Lin D, Wyatt AW, Xue H, Wang Y, Dong X, Haegert A, et al. High fidelity patient-derived xenografts for accelerating prostate cancer discovery and drug development. Cancer Res 2014;74:1272–83.
31. Lee JK, Phillips JW, Smith BA, Park JW, Stoyanova T, McCaffrey EF, et al. N-Myc drives neuroendocrine prostate cancer initiated from human prostate epithelial cells. Cancer Cell 2016;29:536–47.
32. Aparicio AM, Harzstark AL, Corn PG, Wen S, Araujo JC, Tu SM, et al. Platinum-based chemotherapy for variant castrate-resistant prostate cancer. Clin Cancer Res 2013;19:3621–30.
33. Epstein JI, Amin MB, Beltran H, Lotan TL, Mosquera JM, Reuter VE, et al. Proposed morphologic classification of prostate cancer with neuroendocrine differentiation. Am J Surg Pathol 2014;38: 756–67.
34. Tsai H, Morais CL, Alshalalfa M, Tan HL, Haddad Z, Hicks J, et al. Cyclin D1 loss distinguishes prostatic small-cell carcinoma from most prostatic adenocarcinomas. Clin Cancer Res 2015;21:5619–29.
35. Tan HL, Sood A, Rahimi HA, Wang W, Gupta N, Hicks J, et al. Rb loss is characteristic of prostatic small cell neuroendocrine carcinoma. Clin Cancer Res 2014;20:890–903.
36. Thang SP, Violetc J, Sandhud S, Iravania A, Akhursta T, Kong G, et al. Poor outcomes for patients with metastatic castration-resistant prostate cancer with low prostate-specific membrane antigen (PSMA) expression deemed ineligible for 177 Lu-labelled PSMA radioligand therapy. 2018.
37. Sequist LV, Waltman BA, Dias-Santagata D, Digumarthy S, Turke AB, Fidias P, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. Sci Transl Med 2011;3:75ra26.
38. Imakita T, Fujita K, Kanai O, Terashima T, Mio T. Small cell lung cancer transformation during immunotherapy with nivolumab: a case report. Respir Med Case Rep 2017;21:52–5.
39. George J, Lim JS, Jang SJ, Cun Y, Ozretić L, Kong G, et al. Comprehensive genomic profiles of small cell lung cancer. Nature 2015;524:47–53.
40. Niederst MJ, Sequist LV, Poirier JT, Mermel CH, Lockerman EL, Garcia AR, et al. RB loss in resistant EGFR mutant lung adenocarcinomas that transform to small-cell lung cancer. Nat Commun 2015;6:6377.
41. Lee JK, Lee J, Kim S, Youk J, Park S, An Y, et al. Clonal history and genetic predictors of transformation into small-cell carcinomas from lung adenocarcinomas. J Clin Oncol 2017;35:3065–74.
42. Tirosh I, Izar B, Prakadan SM, Wadsworth MH, Treacy D, Trombetta JJ, et al. Dissecting the multicellular ecosystem of metastatic melanoma by single-cell RNA-seq. Science 2016;352:189–96.
43. Kim IS, Heilmann S, Kansler ER, Zhang Y, Zimmer M, Ratnakumar K, et al. Microenvironment-derived factors driving metastatic plasticity in melanoma. Nat Commun 2017;8:14343.
44. Rambow F, Rogiers A, Marin-Bejar O, Aibar S, Femel J, Dewaele M, et al. Toward minimal residual disease-directed therapy in melanoma. Cell 2018;174:843–55.e19.
45. Farrell AS, Joly MM, Allen-Petersen BL, Worth PJ, Lanciault C, Sauer D, et al. MYC regulates ductal-neuroendocrine lineage plasticity in pancreatic ductal adenocarcinoma associated with poor outcome and chemoresistance. Nat Commun 2017;8:1728.
46. Korkaya H, Liu S, Wicha MS. Breast cancer stem cells, cytokine networks, and the tumor microenvironment. J Clin Invest 2011;121:3804–9.

HHS Public Access

Author manuscript

JCO Precis Oncol. Author manuscript; available in PMC 2019 May 21.

Published in final edited form as:

JCO Precis Oncol. 2019 ; 3: . doi:10.1200/PO.18.00327.

CORRESPONDING AUTHOR Michael T. Schweizer, University of Washington, 825 Eastlake Ave E, Seattle, WA 98109; Twitter: @UCalgaryMed, @HopkinsKimmel, schweize@uw.edu.

AUTHOR CONTRIBUTIONS

Conception and design: Michael T. Schweizer, Emmanuel S. Antonarakis, Peter S. Nelson, Tamara L. Lotan, Colin C. Pritchard
Financial support: Michael T. Schweizer, Peter S. Nelson, Colin C. Pritchard
Administrative support: Michael T. Schweizer, Nola Klemfuss, Colin C. Pritchard
Provision of study materials or patients: Michael T. Schweizer, Emmanuel S. Antonarakis, Nola Klemfuss, Elahe A. Mostaghel, Peter S. Nelson, Evan Y. Yu, R. Bruce Montgomery, Tamara L. Lotan
Collection and assembly of data: Michael T. Schweizer, Tarek A. Bismar, Liana B. Guedes, Heather H. Cheng, Maria S. Tretiakova, Funda Vakar-Lopez, Nola Klemfuss, Eric Q. Konnick, Elahe A. Mostaghel, Andrew C. Hsieh, Evan Y. Yu, R. Bruce Montgomery, Lawrence D. True, Tamara L. Lotan, Colin C. Pritchard
Data analysis and interpretation: Michael T. Schweizer, Emmanuel S. Antonarakis, Liana B. Guedes, Heather H. Cheng, Eric Q. Konnick, Peter S. Nelson, Evan Y. Yu, R. Bruce Montgomery, Lawrence D. True, Jonathan I. Epstein, Tamara L. Lotan, Colin C. Pritchard
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/po/author-center.

Michael T. Schweizer
Consulting or Advisory Role: Janssen
Research Funding: Janssen (Inst), AstraZeneca (Inst), Roche (Inst), Pfizer (Inst), Zenith Epigenetics (Inst), Madison Vaccines (Inst)
Emmanuel S. Antonarakis
Honoraria: Sanofi, Dendreon, Medivation, Janssen Biotech, ESSA, Astellas Pharma, Merck, AstraZeneca, Clovis Oncology
Consulting or Advisory Role: Sanofi, Dendreon, Medivation, Janssen Biotech, ESSA, Astellas Pharma, Merck, AstraZeneca, Clovis Oncology
Research Funding: Janssen Biotech (Inst), Johnson & Johnson (Inst), Sanofi (Inst), Dendreon (Inst), Aragon Pharmaceuticals (Inst), Exelixis (Inst), Millennium (Inst), Genentech (Inst), Novartis (Inst), Astellas Pharma (Inst), Tokai Pharmaceuticals (Inst), Merck (Inst), AstraZeneca (Inst), Clovis Oncology (Inst), Constellation Pharmaceuticals (Inst)
Patents, Royalties, Other Intellectual Property: Co-inventor of a biomarker technology that has been licensed to Qiagen
Travel, Accommodations, Expenses: Sanofi, Dendreon, Medivation
Heather H. Cheng
Research Funding: Inovio Pharmaceuticals (Inst), Sanofi (Inst), Astellas Medivation (Inst), Janssen (Inst), Clovis Oncology (Inst), Color Foundation (Inst)
Eric Q. Konnick
Honoraria: Ventana Medical Systems
Travel, Accommodations, Expenses: Ventana Medical Systems
Elahe A. Mostaghel
Research Funding: Context Therapeutics (Inst)
Andrew C. Hsieh
Honoraria: Hotspot Therapeutics
Research Funding: eFFECTOR (Inst)
Patents, Royalties, Other Intellectual Property: MTOR modulators and uses thereof–patent number: 9629843, use of translational profiling to identify target molecules for therapeutic treatment–publication number: 20140288097
Peter S. Nelson
Consulting or Advisory Role: Janssen Oncology, Astellas Pharma, Genentech
Expert Testimony: Veneble-Fitzpatrick Law Firm
Travel, Accommodations, Expenses: Janssen Oncology
Evan Y. Yu
Consulting or Advisory Role: Janssen, Bayer, Merck, AstraZeneca, EMD Serono, Churchill Pharmaceuticals, Incyte, Amgen, Tolmar, QED, Dendreon, Seattle Genetics, Agensys (Inst), Astellas Pharma (Inst), Dendreon (Inst), Genentech (Inst), Bayer (Inst), Merck (Inst), Seattle Genetics (Inst)
R. Bruce Montgomery
Research Funding: ESSA, Medivation/Astellas, Janssen Oncology, Ferring, AstraZeneca
Lawrence D. True
Stock and Other Ownership Interests: Lightspeed Micro
Research Funding: Ventana Medical Systems
Patents, Royalties, Other Intellectual Property: Lens on an open-top lightsheet microscope
Jonathan I. Epstein

Genomic Characterization of Prostatic Ductal Adenocarcinoma Identifies a High Prevalence of DNA Repair Gene Mutations

Michael T. Schweizer, MD[#1,2], **Emmanuel S. Antonarakis, MD**[#3], **Tarek A. Bismar, MD**[4], **Liana B. Guedes, MD**[3], **Heather H. Cheng, MD, PhD**[1,2], **Maria S. Tretiakova, MD, PhD**[1], **Funda Vakar-Lopez, MD**[1], **Nola Klemfuss, MHA**[2], **Eric Q. Konnick, MD, MS**[1], **Elahe A. Mostaghel, MD, PhD**[1,2], **Andrew C. Hsieh, MD**[2], **Peter S. Nelson, MD**[2], **Evan Y. Yu, MD**[1,2], **R. Bruce Montgomery, MD**[1], **Lawrence D. True, MD**[1], **Jonathan I. Epstein, MD**[3], **Tamara L. Lotan, MD**[#3], and **Colin C. Pritchard, MD, PhD**[#1]

[1]University of Washington, Seattle, WA

[2]Fred Hutchinson Cancer Research Center, Seattle, WA

[3]Johns Hopkins University, Baltimore, MD

[4]University of Calgary, Calgary, Alberta, Canada

[#] These authors contributed equally to this work.

Abstract

PURPOSE—Ductal prostate cancer (dPC) is a rare variant of prostatic adenocarcinoma associated with poor outcomes. Although its histopathologic features are well characterized, the underlying molecular hallmarks of this aggressive subtype are not well described. We sought to provide a comprehensive overview of the spectrum of mutations associated with dPC.

METHODS—Three case series across multiple institutions were assembled. All patients had a diagnosis of dPC, and histopathologic classification was confirmed by an expert genitourinary pathologist. Case series 1 included men who were prospectively enrolled in a tumor sequencing study at the University of Washington (n = 22). Case series 2 and 3 included archival samples from men treated at Johns Hopkins Hospital (n = 21) and University of Calgary (n = 8), respectively. Tumor tissue was sequenced on a targeted next-generation sequencing assay, UW-OncoPlex, according to previously published methods. The frequency of pathogenic/likely pathogenic mutations are reported.

RESULTS—Overall, 25 patients (49%) had at least one DNA damage repair gene alteration, including seven (14%) with a mismatch repair gene mutation and 16 (31%) with a homologous repair mutation. Germline autosomal dominant mutations were confirmed or suspected in 10

Consulting or Advisory Role: Dianon, PathAI, Knowerror
Tamara L. Lotan
Consulting or Advisory Role: Janssen Oncology
Research Funding: Ventana Medical Systems
No other potential conflicts of interest were reported.

ASSOCIATED CONTENT
Data Supplement
Author affiliations and support information (if applicable) appear at the end of this article.

patients (20%). Activating mutations in the PI3K pathway (n = 19; 37%), WNT pathway (n = 16; 31%), and MAPK pathway (n = 8; 16%) were common.

CONCLUSION—This study strongly suggests that dPCs are enriched for actionable mutations, with approximately 50% of patients demonstrating DNA damage repair pathway alteration(s). Patients with dPC should be offered next-generation sequencing to guide standard-of-care treatment (eg, immune checkpoint inhibitors) or triaged toward an appropriate clinical trial (eg, poly [ADP-ribose] polymerase inhibitors).

INTRODUCTION

Ductal prostate cancer (dPC) is a rare prostate cancer variant characterized by large glands lined by tall, pseudostratified, columnar, neoplastic epithelial cells, typically arranged over fibrovascular cores or cribriform glands and associated with an aggressive clinical course.[1–3] Outcomes for dPC generally mirror those of Gleason score 4 + 4 = 8 carcinomas, and tumors with at least 10% ductal morphology have been found to associate with a higher stage and suboptimal response to androgen deprivation.[2,3] Overall, approximately 3% of all prostate cancers have some component of ductal histology.[2,4]

Although the histologic features of dPC are well described, there is relatively little information regarding the underlying molecular alterations associated with this prostate cancer subtype. Fluorescence in situ hybridization studies have found that *TMPRSS2:ERG* fusions are present in 10% to 50% of patients with dPC, and ERG protein expression (consistent with *TMPRSS2:ERG* fusions) is also present in this range.[5–8] Limited gene expression profiling studies have found similarities between dPC and patients with acinar tumors, and there is molecular evidence that concurrent ductal and acinar tumors are clonally related.[4,9,10] More recent immunohistochemical profiling studies have demonstrated that positive phospho–mammalian target of rapamycin staining correlated with risk of biochemical recurrence in patients with ductal carcinoma.[11] In a separate study, it was found that loss of PTEN protein expression occurred more frequently in dPC compared with acinar adenocarcinoma, again, potentially implicating mammalian target of rapamycin signaling pathway in the pathobiology of dPC. However, these data remain controversial, because other studies have suggested a lower rate of PTEN protein loss in ductal carcinomas compared with Gleason score 8 acinar carcinomas.[6] More recently, a study evaluating genomic and transcriptomic differences between foci of ductal and acinar prostatic carcinoma from the same individual found enrichment for mutations in *CTNNB1* and *PTEN* within the ductal foci, with associated WNT- or PI3K- pathway activation.[9]

Given the rarity of dPC and the relative lack of information regarding the associated molecular features, we compiled a multi-institutional, international cohort of patients with dPC for targeted next-generation sequencing (NGS). We previously reported the NGS results from a small series characterizing patients with dPC at our institution (University of Washington [UW]).[12] In that preliminary study, we observed a high rate of DNA damage repair (DDR) mutations, including loss-of-function mutations in mismatch repair (MMR) genes. Building from our initial case series, we now report sequencing results from an expanded multiinstitutional collaborative cohort of 51 patients with dPC.

METHODS

Study Populations

We assembled three case series comprising 51 patients with dPC from institutions in the United States and Canada (Data Supplement). Histopathologic classification of all tumors was confirmed by an expert genitourinary pathologist at each institution. All tumor tissue was sequenced on the targeted NGS assay UW-OncoPlex according to previously published methods.[12,13]

Case series 1 consisted of prostate cancer specimens (radical prostatectomies and needle biopsies of prostate and metastatic tumors) from 22 men actively receiving treatment at the University of Washington/Seattle Cancer Care Alliance who were prospectively identified as having a diagnosis of dPC. Tissue used for sequencing was acquired between January 2015 and March 2017. Preliminary sequencing results from this series have been previously published.[12] All men provided informed consent to have their tissue sequenced as part of this study.

Case series 2 included 21 radical prostatectomy samples. A subset was obtained from a tissue microarray composed of primary prostatectomy specimens from men with either dPC (n = 51) or Gleason pattern 4 acinar prostatic adenocarcinoma (n = 75) treated at Johns Hopkins Hospital (JHH) between 1984 and 2004. Details regarding this tissue microarray have been previously published.[14] Additional patients with a ductal carcinoma in the dominant nodule were procured from consecutive radical prostatectomies performed at JHH. Case series 3 included archival tissue from eight men treated by transurethral resection of the prostate at the University of Calgary.

Blinded Morphologic Evaluation

To reevaluate the morphologic classification of all patients in a blinded manner, an expert genitourinary pathologist (J.I.E.) examined scanned digital images of a representative slide from each patient corresponding to the formalin-fixed paraffin-embedded (FFPE) block that was macrodissected for sequencing. Each patient was scored for percentage of the tumor that had ductal morphology overall, as well as the percentage of several described morphologic subtypes of ductal carcinoma: cribriform, papillary, gland-like, prostatic intraepithelial neoplasia–like and solid.

Macrodissection of Tumor Tissue

All tissue was previously FFPE. Hematoxylin and eosin– stained sections served as templates for either macro-dissecting the dPC component from 10-micron sections or obtaining 5.0-×−0.6-mm punches from regions with the highest percentage of dPC.

Next-Generation Sequencing

For all patients, DNA was extracted from macrodissected FFPE samples and sequenced using the targeted NGS platform UW-OncoPlex, as that which interrogates approximately 1.8 Mb of DNA encompassing 262 genes. Briefly, genomic libraries were made from 500 ng of genomic DNA extracted from prostate tumor FFPE tissue and a custom Agilent (Santa

Clara, CA) SureSelect XT capture set used for target enrichment and sequenced on an Illumina (San Diego, CA) NextSEquation 500 instrument with paired-end 101 bp reads. A custom bioinformatics pipeline detects single nucleotide variants, indels of all sizes, structural rearrangements, *PMS2* pseudogene disambiguation, and copy number changes. Sequencing interpretation was performed by an expert molecular pathologist (C.C.P.). Reported alterations were limited to those deemed pathogenic or likely pathogenic (eg, loss of function mutations in tumor suppressors, activating mutations in genes involved in oncogenic signaling pathways).

All 262 genes in UW-OncoPlex were thoroughly reviewed for potential pathogenic germline mutations by an expert in clinical germline cancer predisposition testing (C.C.P.). All reported confirmed or suspected germline variants were carefully vetted by a team expert in variant classification comprising at least three individuals, per the usual clinical process. Of 18 suspected pathogenic germline mutations, 13 were confirmed in nontumor tissue. Of the five suspected germline mutations that did not have matched nontumor DNA, one additional patient was felt to represent a germline mutation after expert molecular pathologist review through cross-referencing against the ClinVar database and by multivariable analysis of the variant allele fraction in the context of tumor content, ploidy, and loss of heterozygosity status.[15,16]

RESULTS

Patient Characteristics

Across the three cohorts (N_{total} = 51), the median age at the time of diagnosis/tissue acquisition was 67.5 years. The majority of patients with data on tumor stage (23 of 40; 57.5%) had T3 or higher disease. For patients with clinical follow-up (UW and University of Calgary, n = 28), seven (25%) were deceased, and 12 (43%) had developed metastatic disease during long-term follow-up. Additional demographics details are listed in Table 1.

dPC Genomics

Overall, our combined cohort of patients with dPC demonstrated a high number of recurrent genomic alterations (Fig 1; Data Supplement). These included alterations in genes involved in DDR repair (n = 24; 47%), PI3K pathway (n = 19; 37%), WNT-signaling pathway (n = 16; 31%), and MAPK signaling (n = 8; 16%). A large number of patients also had mutations in *FOXA1* (n = 17; 33%), *TP53* (n = 9; 18%), and *SPOP* (n = 6; 12%).

Recurrent DDR alterations.—Twenty-five (49%) of 51 patients had at least one alteration in a DDR pathway gene. Overall, seven of 51 patients (14%) had evidence of MMR alterations, six of whom had evidence of hypermutation (ie, ≥ 10 mutation per megabase), consistent with deficient MMR (one patient with monoallelic loss of *MSH2* was not hypermutated). Three patients with MMR alterations also had concurrent secondary mutations in homologous recombination (HR) pathway genes. Sixteen patients (31%) had an HR mutation in the absence of a concurrent MMR mutation. An additional patient with a hotspot *POLD1* mutation was ultramutated (ie, > 100 mutations per megabase).[17,18] There were 10 patients (20%) with evidence of a pathogenic autosomal dominant germline

alteration in a DDR gene, which is significantly higher than reported by The Cancer Genome Atlas for patients with primary prostate cancer (20% *v* 5%; *P* <.001) and numerically higher than unselected patients with metastatic prostate cancer (20% *v* 12%; *P* = .105).[19,20] Of note, two individuals in our dPC cohort were carriers of recessive germline alterations in DDR pathway genes—one with an *ERCC2* alteration and the other with an *MUTYH* alteration. Neither had evidence that the second allele was affected in tumor tissue. Compared with published genomic data from men with localized and castration-resistant prostate cancer (CRPC), our combined cohort of men with dPC was significantly enriched for mutations in DDR genes (both MMR and HR genes), as well as other genes of interest (Table 2).[20,21]

Additional recurrent genomic alterations.—Similar to localized and metastatic CRPC, mutations in *FOXA1* were frequently observed (n = 17; 33%).[20,21] Interestingly, mutations in genes involved in WNT signaling were also frequent (n = 16; 31%). This includes activating/stabilizing mutations in *CTNNB1* (n = 4), as well as inactivating mutations in *APC* (n = 12), a negative regulator of WNT pathway activation. Similar to a prior report, we found that *PTEN* alterations were generally mutually exclusive of mutations in genes associated with WNT-signaling activation (eg, *APC* and *CTNNB1* mutations), although there was one patient with a pathogenic *MSH2* mutation that had secondary alterations in *APC*, *PTEN*, and *PIK3R1*.[9] There were three additional patients in whom WNT-pathway alterations co-occurred with PI3K-pathway alterations, including one patient with an *APC* and *PIK3CA* mutation, and two patients with *CTNNB1* and *PIK3CA* mutations. Compared with patients with CRPC, there were fewer *PTEN* alterations and more *PIK3CA* mutations in our dPC cohort, with an overall similar incidence of PI3K-pathway alterations (Table 2). Alterations in *AR* were infrequent (n = 4; 8%); however, the majority of tissue samples sequenced were primary prostate tissue that had not been exposed to hormonal therapies. *ETS* fusions were significantly less common in our dPC cohort compared with patients with both localized and CRPC (Table 2).

Pathology correlates.—We have previously reported discordance between expert genitourinary pathologists in diagnosing dPC.[24] As such, we performed a secondary pathologic review on available patients. Overall, 46 of the patients (94%) included in this analysis had slides available for central pathologic review (performed by J.I.E. at JHH). Of five ductal histologic subtypes (ie, cribriform, papillary, gland-like, prostatic intraepithelial neoplasia–like, and solid), cribriform (n = 22), and papillary (n = 23) were the most common, and 16 patients showed multiple histologic subtypes present. Although the quantity of dPC in each patient varied, there was no evidence that percentage of ductal involvement correlated with the underlying mutational profile, and a high frequency of DDR mutations was observed regardless of the overall quantity of dPC reported on secondary pathology review (Table 3).

DISCUSSION

To our knowledge, this is the largest cohort of dPC to be examined by NGS. We confirmed that dPCs are enriched for actionable mutations and, remarkably, found that almost half had at least one alteration in a DDR pathway gene. When compared with contemporary prostate

cancer cohorts, we noted significant differences in the mutational profile of dPCs. For instance, in contrast to the Stand Up 2 Cancer–Prostate Cancer Foundation International Prostate Cancer Dream Team discovery set, which reported pathogenic DDR mutations in approximately 25% of unselected patients with metastatic CRPC, we found a significantly higher frequency of DDR alterations in dPCs, including loss-of-function mutations in MMR genes.[21] In addition, because the vast majority of patients included in this analysis had primary tissue sequenced (48 of 51 patients), it is likely that DDR alterations are early, truncal events, which can be easily identified by sequencing archival tissue, negating the need to obtain fresh metastatic tissue in men with more advanced disease. Although we did not intentionally sequence the acinar carcinoma component in patients with mixed ductal-acinar tumors, the fact that concurrent ductal and acinar carcinomas share common ERG rearrangements and other alterations suggests that the DDR alterations are likely shared between these components as well.[4,9] This study adds to the literature suggesting that aggressive histologic subtypes of localized prostate cancer (eg, primary Gleason pattern 5 acinar carcinomas, small cell carcinomas, and now dPCs) may be enriched for MMR defects.[25]

It is also notable that in addition to DDR alterations, there were a number of recurrently mutated genes, including those involved in WNT-and PI3K-signaling pathways. Interestingly, and consistent with prior work from our group, we found that PI3K-signaling alterations occurred more commonly in ductal carcinoma via *PIK3CA* mutations than by *PTEN* gene alterations, which is in contrast to unselected patients with metastatic CRPC.[6,21] These findings are also consistent with a recent report examining genomic and transcriptomic differences between dPC and acinar prostate cancer foci from the same individual.[9] However, in that report, it is worth noting that the authors did not observe enrichment for MMR alterations, and DDR alterations were relatively infrequent. Whether this is due to differences between the two series or the fact that their sample size was relatively small (10 patients) is not clear. We also confirmed that ETS gene rearrangements were significantly less common in patients with dPC compared with both primary (The Cancer Genome Atlas) and metastatic (Stand Up 2 Cancer–Prostate Cancer Foundation) patients with prostate cancer.[4] Importantly, because the NGS panel used in this study (UW-OncoPlex) provides intronic gene coverage for rearrangement hotspot areas in TMPRSS2 and other recurrently rearranged genes, it has a higher degree of sensitivity for detecting ETS fusions and other complex genomic rearrangements that could be missed by panels that only sequence exonic regions.[13,26] These findings indicate that alternative drivers may underlie dPC biology.

Another interesting observation was the apparent enrichment in patients with dPC for germline DDR gene alterations. A previous study had suggested that men with germline DDR mutations (particularly HR mutations) were more likely to harbor components of ductal or intraductal histology than those with pure acinar histology (48% *v* 12%; $P < .01$), although it is recognized that ductal and intraductal features are considered to be histologically distinct.[27] In the current analysis, the prevalence of pathogenic or likely pathogenic germline DDR lesions was 20% (10 of 51), significantly higher than that observed in primary prostate cancers (20% *v* 5%; $P < .001$) or even in unselected sporadic metastatic prostate cancers (20% *v* 12%; $P = .105$).[19,20] Taken together with the previous

study, these findings suggest that patients with dPC should be preferentially offered germline genetic testing even in the absence of metastatic disease. Indeed, knowledge of germline status in the localized disease setting could afford opportunities for modifying management and improving outcomes before metastases develop.

There were important differences between the cohorts included in this analysis. The JHH and Calgary cohorts were assembled from archival tissue and were highly selected. In contrast, the UW cohort comprised prospectively identified men receiving care for prostate cancer in the clinic, and thus represented a real-world example of selecting patients for sequencing on the basis of histology. Another key difference is that the JHH cohort only included patients who underwent prostatectomy, and no long-term follow-up data were available. Given that all patients in the JHH cohort were considered to be prostatectomy candidates, this raises the possibility that these men had less aggressive disease, especially in light of the fact that 70% of men in the Calgary and UW cohorts either died or developed metastatic disease.

It is also notable that the UW cohort included a number of patients who were disputed in terms of whether dPC was present, and overall, 12 patients (26%) included in this series who underwent secondary pathology review were felt to not contain significant ductal features (n = 11 from UW and n = 1 from JHH). It is important to bear in mind,Ductal Prostate Cancer Genomics however, that all patients included in this analysis were believed to contain a component of ductal histology by at least one expert genitourinary pathologist. In addition, because slides from UW were not scanned before macrodissecting the ductal component, we cannot exclude the possibility that the slides sent for secondary review were not representative of the slides used for sequencing. In addition, the observed interpathologist variance is consistent with prior experience evaluating patients with dPC.[28] Importantly, there were no clear differences in mutational profiles for patients felt to not possess a clear ductal component on secondary pathology review or between patients with pure versus mixed ductal histology (Table 3). Larger studies aimed at evaluating differences between patients with pure and mixed dPC and studies evaluating differences between ductal and acinar foci from the same patient are warranted but are beyond the scope of this study.

In conclusion, despite the heterogeneity of our cohort, these results indicate that patients with any fraction of dPC should be offered NGS, given that the presence of dPC histology can serve as a rapid means to select patients enriched for actionable mutations, particularly in MMR and HR genes. On the basis of this analysis, nearly half would qualify for treatment with investigational poly (ADP-ribose) polymerase inhibitors, platinum-based chemotherapy, and/or an immune checkpoint inhibitor.[29–34]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

SUPPORT

Supported by National Cancer Institute Grant No. P30 CA015704 and Pacific Northwest Prostate Cancer Grant No. SPORE CA097186. M.T.S. is supported by a Prostate Cancer Foundation Young Investigator Award and Department of Defense Award W81XWH-16-1-0484. C.C.P. is supported in part by the Prostate Cancer Foundation, a Department of Defense Prostate Cancer Research Program Award PC131820, and the Institute for Prostate Cancer Research. E.S.A. is partially supported by National Institutes of Health Grants No. R01 CA185297 and P30 CA006973 and Department of Defense Prostate Cancer Research Program Grant No. W81XWH-15-2-0050. A.C.H. is a V Foundation Scholar and is funded by a NextGen Grant for Transformative Cancer Research from the American Association for Cancer Research and a Burroughs Wellcome Fund Career Award for Medical Scientists.

REFERENCES

1. WHO: Classification of Tumours of the Urinary System and Male Genital Organs (ed 4). Geneva, Switzerland, World Health Organization, 2016
2. Humphrey PA: Histological variants of prostatic carcinoma and their significance. Histopathology 60:59–74, 2012 [PubMed: 22212078]
3. Brinker DA, Potter SR, Epstein JI: Ductal adenocarcinoma of the prostate diagnosed on needle biopsy: Correlation with clinical and radical prostatectomy findings and progression. Am J Surg Pathol 23:1471–1479, 1999 [PubMed: 10584700]
4. Lotan TL, Toubaji A, Albadine R, et al.: TMPRSS2-ERG gene fusions are infrequent in prostatic ductal adenocarcinomas. Mod Pathol 22:359–365, 2009 [PubMed: 19151660]
5. Han B, Mehra R, Suleman K, et al.: Characterization of ETS gene aberrations in select histologic variants of prostate carcinoma. Mod Pathol 22:1176–1185, 2009 [PubMed: 19465903]
6. Morais CL, Herawi M, Toubaji A, et al.: PTEN loss and ERG protein expression are infrequent in prostatic ductal adenocarcinomas and concurrent acinar carcinomas. Prostate 75:1610–1619, 2015 [PubMed: 26178158]
7. Vinceneux A, Bruyere F, Haillot O, et al.: Ductal adenocarcinoma of the prostate: Clinical and biological profiles. Profile 77:1242–1250, 2017
8. Chaux A, Albadine R, Toubaji A, et al.: Immunohistochemistry for ERG expression as a surrogate for TMPRSS2-ERG fusion detection in prostatic adeno-carcinomas. Am J Surg Pathol 35:1014–1020, 2011 [PubMed: 21677539]
9. Gillard M, Lack J, Pontier A, et al.: Integrative genomic analysis of coincident cancer foci implicates CTNNB1 and PTEN alterations in ductal prostate cancer. Eur Urology Focus 10.1016/j.euf.2017.12.003 [epub ahead of print on December 8, 2017]
10. Sanati S, Watson MA, Salavaggione AL, et al.: Gene expression profiles of ductal versus acinar adenocarcinoma of the prostate. Mod Pathol 22:1273–1279, 2009 [PubMed: 19633648]
11. Jeong SU, Kekatpure AK, Park JM, et al.: Diverse immunoprofile of ductal adenocarcinoma of the prostate with an emphasis on the prognostic factors. J Pathol Transl Med 51:471–481, 2017 [PubMed: 28793393]
12. Schweizer MT, Cheng HH, Tretiakova MS, et al.: Mismatch repair deficiency may be common in ductal adenocarcinoma of the prostate. Oncotarget 7:82504–82510, 2016 [PubMed: 27756888]
13. Pritchard CC, Salipante SJ, Koehler K, et al.: Validation and implementation of targeted capture and sequencing for the detection of actionable mutation, copy number variation, and gene rearrangement in clinical cancer specimens. J Mol Diagn 16:56–67, 2014 [PubMed: 24189654]
14. Herawi M, Epstein JI: Immunohistochemical antibody cocktail staining (p63/HMWCK/AMACR) of ductal adenocarcinoma and Gleason pattern 4 cribriform and noncribriform acinar adenocarcinomas of the prostate. Am J Surg Pathol 31:889–894, 2007 [PubMed: 17527076]
15. Li MM, Datto M, Duncavage EJ, et al.: Standards and guidelines for the interpretation and reporting of sequence variants in cancer: A joint consensus recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. J Mol Diagn 19:4–23, 2017 [PubMed: 27993330]
16. Shirts BH, Casadei S, Jacobson AL, et al.: Improving performance of multigene panels for genomic analysis of cancer predisposition. Genet Med 18:974–981, 2016 [PubMed: 26845104]
17. Rayner E, van Gool IC, Palles C, et al.: A panoply of errors: Polymerase proofreading domain mutations in cancer. Nat Rev Cancer 16:71–81, 2016 [PubMed: 26822575]

18. Shlien A, Campbell BB, de Borja R, et al.: Combined hereditary and somatic mutations of replication error repair genes result in rapid onset of ultra-hypermutated cancers. Nature Genet 47:257–262, 2015 [PubMed: 25642631]
19. Pritchard CC, Mateo J, Walsh MF, et al.: Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med 375:443–453, 2016 [PubMed: 27433846]
20. The Cancer Genome Atlas Research Network: The molecular taxonomy of primary prostate cancer. Cell 163:1011–1025, 2015 10.1016/j.cell.2015.10.025 [PubMed: 26544944]
21. Robinson D, Van Allen EM, Wu YM: Integrative clinical genomics of advanced prostate cancer. Cell 161:1215–1228, 2015 10.1016/j.cell.2015.05.001 [PubMed: 26000489]
22. Gao J, Aksoy BA, Dogrusoz U, et al.: Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. Sci Signal 6:pl1, 2013 [PubMed: 23550210]
23. Cerami E, Gao J, Dogrusoz U, et al.: The cBio cancer genomics portal: An open platform for exploring multidimensional cancer genomics data. Cancer Discov 2:401–404, 2012 [PubMed: 22588877]
24. True L, Gulati R, Lange J, et al.: Histological patterns of ductal adenocarcinoma of prostate correlates with mutations in DNA repair genes and may aid in selecting the type of systemic therapy for castration-resistant prostate carcinoma. Presented at the USCAP Annual Meeting San Antonio, TX, March 4–10, 2017
25. Guedes LB, Antonarakis ES, Schweizer MT, et al.: MSH2 loss in primary prostate cancer. Clin Cancer Res 23:6863–6874, 2017 [PubMed: 28790115]
26. Pritchard CC, Morrissey C, Kumar A, et al.: Complex MSH2 and MSH6 mutations in hypermutated microsatellite unstable advanced prostate cancer. Nat Commun 5:4988, 2014 [PubMed: 25255306]
27. Isaacsson Velho P, Silberstein JL, Markowski MC, et al.: Intraductal/ductal histology and lymphovascular invasion are associated with germline DNA-repair gene mutations in prostate cancer. Prostate 78:401–407, 2018 [PubMed: 29368341]
28. Seipel AH, Delahunt B, Samaratunga H, et al.: Diagnostic criteria for ductal adenocarcinoma of the prostate: Interobserver variability among 20 expert uropathologists. Histopathology 65:216–227, 2014 [PubMed: 24467262]
29. Cheng HH, Pritchard CC, Boyd T, et al.: Biallelic inactivation of BRCA2 in platinum-sensitive metastatic castration-resistant prostate cancer. Eur Urol 69:992–995, 2016 [PubMed: 26724258]
30. Mateo J, Carreira S, Sandhu S, et al.: DNA-repair defects and olaparib in metastatic prostate cancer. N Engl J Med 373:1697–1708, 2015 [PubMed: 26510020]
31. Pennington KP, Walsh T, Harrell MI, et al.: Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube, and peritoneal carcinomas. Clin Cancer Res 20:764–775, 2014 [PubMed: 24240112]
32. US Food and Drug Administration: FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication, https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm560040.htm
33. Le DT, Durham JN, Smith KN, et al.: Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 357:409–413, 2017 [PubMed: 28596308]
34. Le DT, Uram JN, Wang H, et al.: PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 372:2509–2520, 2015 [PubMed: 26028255]

CONTEXT

Key Objective

The key objective was to provide an overview of the genomic alterations associated with ductal prostate cancers.

Knowledge Generated

Ductal prostate cancers are associated with a high incidence of mutations in DNA repair genes. Affected genes include those mediating homologous recombination and mismatch repair pathways.

Relevance

Because mutations in genes involved in DNA repair are highly actionable, sequencing all patients with ductal prostate cancer should be considered.

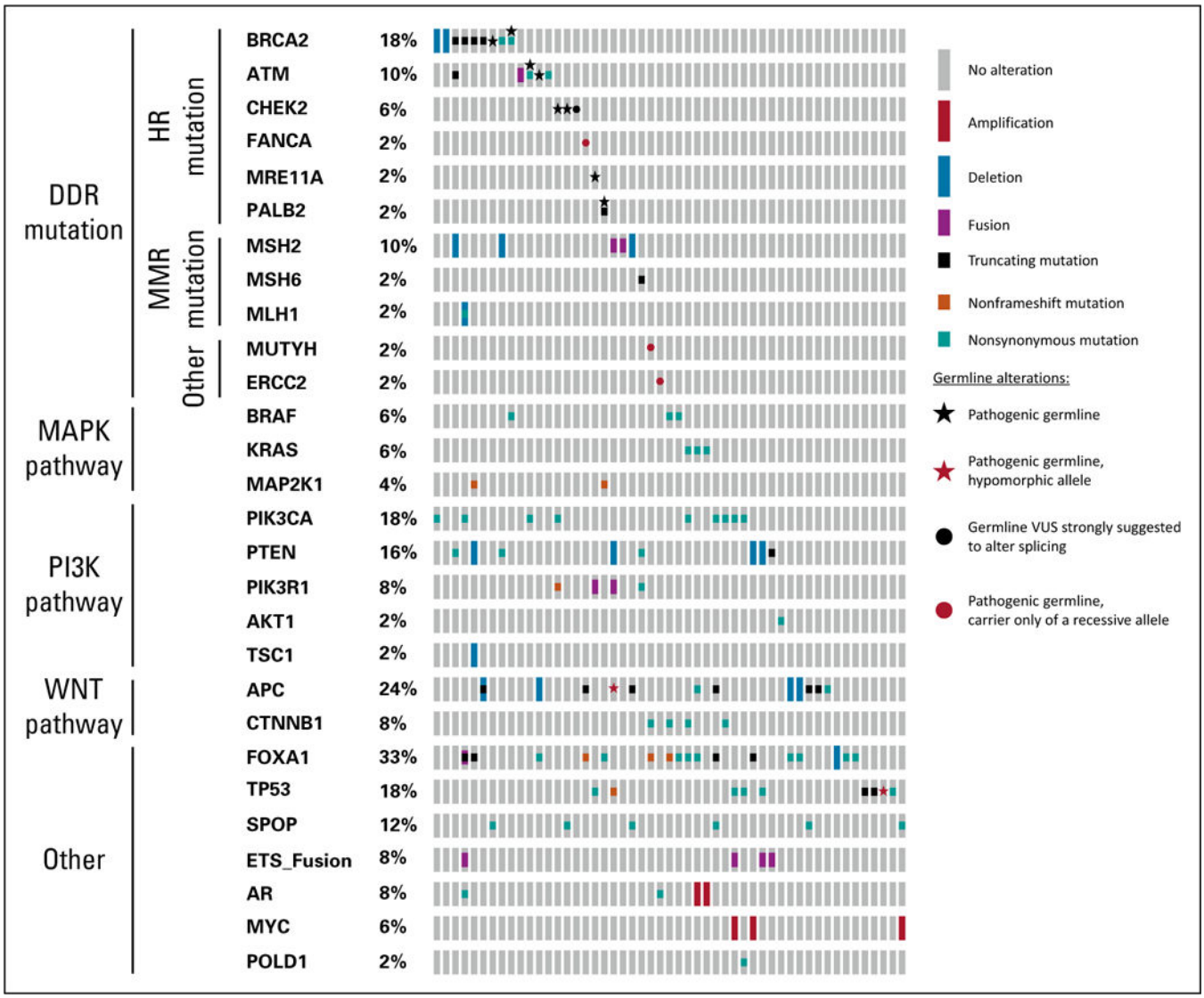


FIG 1.

Landscape of genomic alterations across 51 patients with ductal prostate cancer. Each column represents one patient. Pathogenic mutations were those predicted to either activate oncogenic signaling pathways (eg, WNT-or PI3K-signaling) or inactivate tumor suppressors (eg, DNA damage repair [DDR] genes, *TP53*). HR, homologous recombination; MMR, mismatch repair; VUS, variant of uncertain significance.

TABLE 1.

Demographics and Characteristics

Characteristic	Value
Median age (range), years	67.5 (47–94)
Gleason *	
7	4 (13)
8	7 (23)
9	18 (60)
10	1 (3)
Metastatic disease at presentation †	11 (26)
Source of tissue for sequencing	
TURP	8 (15)
Prostatectomy	29 (56)
Prostate needle biopsy	11 (21)
Metastatic biopsy	3 (6)

NOTE. Data are No. (%) unless otherwise indicated.

Abbreviation: TURP, transurethral resection of the prostate.

* Gleason score was only provided for patients with mixed ductalacinar histology (n = 30).

† Disease state at time of initial presentation was only available for Johns Hopkins Hospital and University of Washington (n = 43).

TABLE 2.

Recurrent Genomic Alterations in Patients With Ductal Prostate Cancer Compared With Men With Sporadic Localized and Castration-Resistant Prostate Cancer [22,23]

	No. of Mutations (% of men)			Ductal Cohort Versus TCGA		Ductal Cohort Versus SU2C	
Gene/Pathway	**Ductal Cohort (n = 51)**	**TCGA (n = 333)***	**SU2C (n = 150)†**	**RR (95% CI)**	***P***	**RR (95% CI)**	***P***
Any DDR	25 (49)	62 (19)	34 (23)	2.63 (1.84 to 3.77)	< .001	2.16 (1.44 to 3.25)	< .001
MMR alteration	7 (14)	11 (3)	3 (2)	4.16 (1.69 to 10.23)	.002	6.86 (1.84 to 25.55)	.004
MSH2	5 (10)	5 (2)	3 (2)	6.53 (1.96 to 21.77)	.002	4.90 (1.21 to 19.79)	.026
MLH1	1 (2)	1 (0.3)	1 (0.7)	6.53 (0.41 to 102.76)	.182	2.94 (0.18 to 46.17)	.443
MSH6	1 (2)	6 (2)	0	1.09 (0.13 to 8.85)	.937	—	.254
PMS2	0	4 (1)	0	—	1.00	—	—
High penetrance HR alterations	15 (29)	44 (13)	29 (19)	2.23 (1.34 to 3.69)	.002	1.52 (0.89 to 2.60)	.125
BRCA1	0	4 (1)	1 (0.7)	—	1.00	—	1.00
BRCA2	9 (18)	11 (3)	19 (13)	5.34 (2.33 to 12.25)	< .001	1.39 (0.67 to 2.88)	.371
ATM	5 (10)	24 (7)	7 (7.3)	1.36 (0.54 to 3.40)	.511	1.34 (0.49 to 3.66)	.572
PALB2	1 (2)	5 (2)	0	1.31 (0.16 to 10.95)	.806	—	.254
WNT pathway	16 (31)	27 (8)	19 (13)	3.87 (2.25 to 6.66)	< .001	2.48 (1.38 to 4.44)	.002
CTNNB1	4 (8)	9 (3)	6 (4)	2.90 (0.93 to 9.08)	.067	1.96 (0.58 to 6.67)	.281
APC	12 (24)	18 (5)	13 (9)	4.35 (2.23 to 8.49)	< .001	2.71 (1.32 to 5.56)	.006
PI3K pathway	19 (38)	103 (31)	73 (49)	1.20 (0.81 to 1.78)	.351	0.77 (0.52 to 1.13)	.182
PTEN	8 (16)	58 (17)	61 (41)	0.90 (0.46 to 1.77)	.762	0.39 (0.20 to 0.75)	.005
PIK3CA	9 (18)	16 (5)	8 (5)	3.67 (1.71 to 7.87)	.001	3.31 (1.35 to 8.12)	.009
PIK3R1	4 (8)	22 (7)	8 (5)	1.19 (0.43 to 3.30)	.743	1.47 (0.46 to 4.68)	.514
AKT1	1 (2)	7 (2)	2 (1)	0.93 (0.12 to 7.43)	.948	1.47 (0.14 to 15.88)	.751
TSC1	1 (2)	5 (2)	2 (1)	1.31 (0.16 to 10.95)	.806	1.47 (0.14 to 15.88)	.751
MAPK pathway	8 (16)	13 (4)	11 (7)	4.02 (1.75 to 9.21)	.001	2.14 (0.91 to 5.02)	.081
BRAF	3 (6)	12 (4)	7 (5)	1.63 (0.48 to 5.59)	.435	1.26 (0.34 to 4.69)	.73
KRAS	3 (6)	1 (0.3)	4 (3)	19.59 (2.08 to 184.72)	.009	2.21 (0.51 to 9.53)	.289
MAP2K1	2 (4)	1 (0.3)	1 (0.7)	13.06 (1.21 to 141.42)	.035	5.88 (0.54 to 63.52)	.144

	No. of Mutations (% of men)			Ductal Cohort Versus TCGA		Ductal Cohort Versus SU2C	
Gene/Pathway	**Ductal Cohort (n = 51)**	**TCGA (n = 333)***	**SU2C (n = 150)†**	**RR (95% CI)**	***P***	**RR (95% CI)**	***P***
Other							
ETS fusions	4 (8)	199 (60)	84 (56)	0.13 (0.05 to 0.34)	< .001	0.14 (0.05 to 0.36)	< .001
POLD1	1 (2)	2 (1)	0	3.26 (0.30 to 35.36)	.330	—	.254
CHEK2	3 (6)	10 (3)	3(2)	1.96 (0.56 to 6.88)	.294	2.94 (0.61 to 14.12)	.178

NOTE. *P* values and RRs are in comparison with the ductal cohort. Mutational frequencies for comparator data sets were derived from either the primary publications or extracted from cBioPortal.[20–23]

Abbreviations: DDR, DNA damage repair; HR, homologous recombination; MMR, mismatch repair; RR, relative risk; SU2C, Stand Up 2 Cancer; TCGA, The Cancer Genome Atlas.

*The TCGA data set comprises 333 men with localized prostate cancer.[20]

†SU2C-PCF International Prostate Cancer Dream Team discovery set comprises 150 men with metastatic castration-resistant prostate cancer. The genomic landscape of this population has been previously published.[21]

TABLE 3.

Key Genomic Features Stratified by Ductal Involvement

Ductal Involvement	No.	Any DDR, No. (%)	*P*	MMR, No. (%)	*P*	HRD, No. (%)	*P*	Germline DDR, No. (%)*	*P*
Ductal features present	12	8 (67)	.314	3 (25)	.173	6 (50)	.37	5 (42)	.265
Ductal features absent	34	15 (44)		3 (9)		12 (35)		7 (23)	
Pure ductal	10	5 (50)	1	1 (10)	1	5 (50)	.489	1 (13)	.402
Not pure ductal	35	18 (51)		5 (14)		13 (37)		11 (32)	

NOTE. Secondary pathology review evaluated for the extent of ductal involvement, and comparative analyses assessing for correlation between key genomic features and extent of ductal histology were performed. One patient classified as positive for ductal involvement did not provide an estimate on percent involvement.

Abbreviations: DDR, DNA damage repair; HRD, homologous recombination deficiency; MMR, mismatch repair.

*Three patients were indeterminate regarding whether the DDR alteration was germline versus somatic and were therefore excluded from this analysis.

Original Article

Real-World Outcomes of Sipuleucel-T Treatment in PROCEED, a Prospective Registry of Men With Metastatic Castration-Resistant Prostate Cancer

Celestia S. Higano, MD[1]; Andrew J. Armstrong, MD, ScM [2,3]; A. Oliver Sartor, MD [4]; Nicholas J. Vogelzang, MD[5]; Philip W. Kantoff, MD[6]; David G. McLeod, MD, JD[7]; Christopher M. Pieczonka, MD[8]; David F. Penson, MD, MPH[9,10]; Neal D. Shore, MD[11]; Jeffrey Vacirca, MD[12]; Raoul S. Concepcion, MD[13]; Ronald F. Tutrone, MD[14]; Luke T. Nordquist, MD[15]; David I. Quinn, MBBS, PhD[16]; Vahan Kassabian, MD[17]; Mark C. Scholz, MD[18]; Matt Harmon, JD[19]; Robert C. Tyler, PhD[20]; Nancy N. Chang, PharmD[20]; Hong Tang, MD[20]; and Matthew R. Cooperberg, MD, MPH[21,22]

BACKGROUND: The large registry, PROVENGE Registry for the Observation, Collection, and Evaluation of Experience Data (PROCEED) (NCT01306890), evaluated sipuleucel-T immunotherapy for asymptomatic/minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC). **METHODS:** PROCEED enrolled patients with mCRPC receiving 3 biweekly sipuleucel-T infusions. Assessments included overall survival (OS), serious adverse events (SAEs), cerebrovascular events (CVEs), and anticancer interventions (ACIs). Follow-up was for ≥3 years or until death or study withdrawal. **RESULTS:** In 2011-2017, 1976 patients were followed for 46.6 months (median). The median age was 72 years, and the baseline median prostate-specific antigen level was 15.0 ng/mL; 86.7% were white, and 11.6% were African American. Among the patients, 1902 had 1 or more sipuleucel-T infusions. The median OS was 30.7 months (95% confidence interval [CI], 28.6-32.2 months). Known prognostic factors were independently associated with OS in a multivariable analysis. Among the 1255 patients who died, 964 (76.8%) died of prostate cancer (PC) progression. The median time from the first infusion to PC death was 42.7 months (95% CI, 39.4-46.2 months). The incidence of sipuleucel-T–related SAEs was 3.9%. The incidence of CVEs was 2.8%, and the rate per 100 person-years was 1.2 (95% CI, 0.9-1.6). The CVE incidence among 11,972 patients with mCRPC from the Surveillance, Epidemiology, and End Results–Medicare database was 2.8%; the rate per 100 person-years was 1.5 (95% CI, 1.4-1.7). One or more ACIs (abiraterone, enzalutamide, docetaxel, cabazitaxel, or radium 223) were received by 77.1% of the patients after sipuleucel-T; 32.5% and 17.4% of the patients experienced 1- and 2-year treatment-free intervals, respectively. **CONCLUSIONS:** PROCEED provides contemporary survival data for sipuleucel-T–treated men in a real-world setting of new life-prolonging agents, which will be useful in discussing treatment options with patients and in powering future trials with sipuleucel-T. The safety and tolerability of sipuleucel-T in PROCEED were consistent with previous findings. ***Cancer* 2019;125: 4172-4180**.

KEYWORDS: immunotherapy, overall survival, prostate cancer, safety.

INTRODUCTION

Sipuleucel-T is an autologous cellular immunotherapy for asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC). In the pivotal phase 3 trial Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT; NCT00065442), sipuleucel-T significantly reduced the risk of death among patients with mCRPC and improved median overall survival (OS) by 4.1 months versus a placebo.[1] Sipuleucel-T is recommended

Corresponding author: Celestia S. Higano, MD, Seattle Cancer Care Alliance, 825 Eastlake Ave (G4830), Seattle, WA 98109-1023; thigano@uw.edu

[1]Division of Medical Oncology, Departments of Medicine and Urology, University of Washington and Fred Hutchinson Cancer Research Center, Seattle, Washington; [2]Division of Medical Oncology, Duke University Medical Center, Duke Cancer Institute, Duke University, Durham, North Carolina; [3]Division of Urology, Duke University Medical Center, Duke Cancer Institute, Duke University, Durham, North Carolina; [4]Section of Hematology and Medical Oncology, Department of Medicine, Tulane Cancer Center and Tulane University School of Medicine, New Orleans, Louisiana; [5]Division of Hematology/Oncology, Comprehensive Cancer Centers of Nevada, Las Vegas, Nevada; [6]Department of Medicine, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, New York; [7]Department of Surgery, Center for Prostate Disease Research at the Uniformed Services of Health Sciences, Bethesda, Maryland; [8]Associated Medical Professionals, Syracuse, New York; [9]Department of Urologic Surgery, Vanderbilt University Medical Center, Nashville, Tennessee; [10]Department of Health Policy, Vanderbilt University Medical Center, Nashville, Tennessee; [11]Department of Urology, Carolina Urologic Research Center, Myrtle Beach, South Carolina; [12]New York Cancer and Blood Specialists, New York, New York; [13]Urology Associates PC, Nashville, Tennessee; [14]Chesapeake Urology, Towson, Maryland; [15]Department of Medical Oncology, GU Research Network, Omaha, Nebraska; [16]Division of Medical Oncology, Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, California; [17]Advanced Urology, Atlanta, Georgia; [18]Prostate Cancer Research Institute, Marina del Rey, California; [19]Department of Biometrics, Dendreon Pharmaceuticals LLC, Seattle, Washington; [20]Department of Medical Affairs, Dendreon Pharmaceuticals LLC, Seattle, Washington; [21]Department of Urology, Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, California; [22]Department of Epidemiology and Biostatistics, Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, California

Additional supporting information may be found in the online version of this article.

DOI: 10.1002/cncr.32445, **Received:** December 19, 2018; **Revised:** July 12, 2019; **Accepted:** July 17, 2019, **Published online** September 4, 2019 in Wiley Online Library (wileyonlinelibrary.com)

across multiple guidelines[2-7] and as a first-line mCRPC treatment option[2,3,7] (category 1 recommendation by the National Comprehensive Cancer Network). In patients with low baseline prostate-specific antigen (PSA) levels (≤22.1 ng/mL) in IMPACT, retrospective analyses demonstrated a 13-month greater improvement in OS with sipuleucel-T versus a placebo.[8]

Sipuleucel-T was generally well tolerated across several prostate cancer (PC) trials.[1,9-14] The most common adverse events (≥15%) were chills, fatigue, fever, back pain, nausea, joint ache, and headache of mostly mild to moderate severity. Incidences of grade 3 and 4 adverse events were 23.6% and 4.0%, respectively, with sipuleucel-T and 25.1% and 3.3%, respectively, with a placebo. Serious adverse events (SAEs) included acute infusion reactions and cerebrovascular events (CVEs).[14] Data from 4 randomized, double-blind, placebo-controlled clinical trials (D9901 [NCT00005947],[12,13] D9902A [NCT01133704],[13] IMPACT,[1] and PROTECT [NCT00779402][9]) showed that CVEs, excluding transient ischemic attacks (TIAs), occurred in 3.5% (sipuleucel-T) and 2.6% (placebo) of patients (not statistically significant).[14] The clinical significance and causal relationship are uncertain.

The PROVENGE Registry for the Observation, Collection, and Evaluation of Experience Data (PROCEED; NCT0136890), evaluated real-world safety data and provided an opportunity to analyze efficacy outcomes of mCRPC management involving sipuleucel-T during a time of rapidly evolving management protocols.

MATERIALS AND METHODS

Study Design and Patients

PROCEED was a multicenter, open-label, observational registry conducted at urology and medical oncology clinics in private practice and at academic sites (see the Supporting Methods section in the supporting information). The primary and secondary objectives were to quantify CVE risk and OS, respectively. SAEs were collected. For a protocol-specified, exploratory objective, the proportion of patients receiving subsequent anticancer interventions (ACIs) was assessed. Both the protocol and its single amendment were approved by each center's Institutional Review Board before patient enrollment. Before participation, patients provided written informed consent.

Treatment

No randomization, blinding, or treatment masking was conducted. Patients underwent a 1.5 to 2.0× blood volume leukapheresis for antigen-presenting cell (APC) isolation with a sipuleucel-T infusion 3 to 4 days later; this was repeated at approximately 2-week intervals for 3 infusions.

Study Procedures

Safety and survival were assessed during normal clinical practice and were reported every 3 months after the final sipuleucel-T infusion. Use of central venous catheters at the physician's discretion was recorded. PROCEED did not require the recording of all PC-related events after sipuleucel-T treatment. ACI use after the first infusion of sipuleucel-T was recorded. Decisions to use further treatment and the choice and timing of ACI use were at the physician's discretion.

All SAEs (according to MedDRA version 19.1) from the first sipuleucel-T infusion through 60 days after the final infusion were captured. Thereafter, SAEs at least possibly related to sipuleucel-T were recorded. All CVE data were collected, regardless of causality, severity, or outcome, throughout PROCEED. CVEs, adjudicated by an independent neurologist, included all strokes (ischemic and hemorrhagic), intracranial hemorrhage, and TIAs (focal neurologic deficit episodes resolving within 24 hours).[15]

Patients were followed for ≥3 years or until death or study withdrawal. The cause of death was reported on a case report form. An end-of-study closeout form was completed to ascertain death. For patients lost to follow-up, sites performed a death-sweep search for obituaries.

Statistical Analyses

The sample size was based on an evaluation of the CVE rate. With ≥1500 patients followed for ≥3 years (4500 person-years), the 95% confidence interval (CI) for estimating the CVE incidence rate per 100 patient-years would have a width of <1 unit as long as the observed rate was <2.8/100 patient-years.[16] For 1500 patients, the probability of observing 1 or more occurrences of a rare event (1 in 1000) would be 0.78. The sample size was increased from 1500 to allow for 4500 person-years of follow-up.

The predefined analysis population was all patients receiving 1 or more full or partial (>0 mL) sipuleucel-T infusions. Endpoints were summarized descriptively unless otherwise stated. All analyses were performed with SAS (versions 9.2 and 9.4; SAS Institute, Inc, Cary, North Carolina).

OS was measured from the date of the first sipuleucel-T infusion for ≥3 years or until the patient had

otherwise gone off the study. If death was not reported, patients were censored from the last study visit. OS data were analyzed with Kaplan-Meier methodology; Cox proportional hazards regression was used to calculate hazard ratios and 95% CIs. These were post hoc analyses with *P* values that were not adjusted for multiplicity. Univariable, stepwise Cox modeling and multivariable analysis were performed to assess for independent baseline predictors of OS that had both clinical and statistical relevance. Variables were selected in a stepwise process for the final multivariable analysis model at a .1 significance level (see the Supporting Methods for more details). The association of OS with natural logarithm–transformed sipuleucel-T product parameters (APC activation, APC cell count, and total nucleated cell count) was estimated with a Cox proportional hazards regression model; statistical significance was a 2-tailed *P* value <.05. A post hoc analysis evaluated OS by baseline PSA quartiles; hazard ratios and 95% CIs were calculated by the Cox regression model.

Primary summarization of CVEs excluded TIAs for consistency with how CVE rates had been previously defined.[14] CVEs including TIAs were summarized separately. The PROCEED CVE incidence was compared with a retrospective analysis of the incidence of first-time CVEs in men 65 years old or older with PC, including those with metastatic PC and a castrated state, within the Surveillance, Epidemiology, and End Results (SEER)–Medicare database in 1999-2013 (see the supporting information).

An exploratory analysis described the proportion of patients receiving ACIs after the first sipuleucel-T infusion. The Kaplan-Meier method estimated the proportion of ACI use at 1 and 2 years.

RESULTS

Patients and Treatment

PROCEED was conducted from January 27, 2011 (the first patient registered), to January 17, 2017 (the last patient visit); 1976 consenting patients were enrolled across 192 sites. Overall, 1902 patients received 1 or more sipuleucel-T infusions: 1248 (65.6%) were treated in oncology practices, and 654 (34.4%) were treated in urology practices. Most patients (79.1%) received sipuleucel-T at 140 community clinics; the remainder received it at 52 academic centers (see the Supporting Results in the supporting information for study discontinuation reasons).

Central venous catheters were used in 891 patients (46.8%). Overall, 1813 patients (95.3%) received 3 sipuleucel-T infusions, 57 (3.0%) received 2, and 32 (1.7%) received 1. Reasons for 3 or fewer infusions included an SAE (34 [1.8%]), other (32 [1.7%]), disease progression after the first infusion (22 [1.2%]), patient refusal (16 [0.8%]; including a refusal to transfer location or answer study questions), and venous access problems (4 [0.2%]). Multiple reasons for noninfusion were possible.

Table 1 lists patient characteristics for PROCEED and for IMPACT sipuleucel-T–treated patients for comparison.[1] The median patient age was 72 years; 86.7% were white, and 11.6% were African American. Most patients had an Eastern Cooperative Oncology Group performance status of 0 or 1. The median baseline PSA level was 15.0 ng/mL (interquartile range, 5.2-46.1 ng/mL). Some patients received prior docetaxel, abiraterone, or enzalutamide (commercially or as an investigational agent). Most had bone-dominant metastases with or without lymph node involvement. The metastatic site or status was not reported for 19 patients (1.0%). Supporting Table 1 lists PROCEED baseline CVE risk factors.

Overall Survival

The median OS was 30.7 months (95% CI, 28.6-32.2 months; Fig. 1); the median follow-up was 46.6 months. During follow-up, 1255 patients (66.0%) died. Death or survival could not be ascertained for 45 patients. The main cause of death was PC progression (964 of 1255 [76.8%]); the median time to PC-specific death was 42.7 months (95% CI, 39.4-46.2 months). Other causes of death were unknown (154 [12.3%]), other (136 [10.8%]), a cardiac event (42 [3.3%]), a CVE (17 [1.4%]), and a new primary cancer (8 [0.6%]). More than 1 cause of death could be recorded for a patient.

A post hoc analysis indicated that the median OS was longer for patients in the lowest baseline PSA quartile (≤5.27 ng/mL) than patients in the second (>5.27 to ≤15.08 ng/mL), third (>15.08 to ≤46 ng/mL), and fourth quartiles (>46 ng/mL): 47.7 months (95% CI, 43.5-50.7 months), 33.2 months (95% CI, 30.9-35.5 months), 27.2 months (95% CI, 24.1-29.8 months), and 18.4 months (95% CI, 15.9-21.2 months), respectively. The hazard ratios for each quartile versus the lowest quartile were 1.6 (95% CI, 1.3-1.9), 2.0 (95% CI, 1.7-2.4), and 3.0 (95% CI, 2.6-3.6), respectively.

Univariable analyses showed that 15 evaluated baseline characteristics were significant predictors of OS (Supporting Table 2). Eleven characteristics were included in the final primary multivariable analysis. Of these, 10 were associated with OS at a significance level

TABLE 1. Demographics, Baseline Disease Characteristics, and Prior Prostate Cancer Treatments in PROCEED and IMPACT[1]

Parameter	PROCEED Safety Population (n = 1902)	IMPACT Sipuleucel-T–Treated Arm (n = 341)
Age, median (range, min-max), y	72 (42-97)	72 (49-91)
Race, No. (%)		
White	1649 (86.7)	305 (89.4)
Black or African American	221 (11.6)	23 (6.7)
Asian	22 (1.2)	2 (0.6)
Other	10 (0.5)	11 (3.2)
ECOG performance status, No. (%)		
0	1265 (66.5)	280 (82.1)
1	571 (30.0)	61 (17.9)
≥2	42 (2.2)	0
Unknown	24 (1.3)	0
Gleason sum reported, No. (%)		
≤7	790 (41.5)	257 (75.4)
≥8	963 (50.6)	84 (24.6)
Unknown	149 (7.8)	0
Charlson Comorbidity Index, No. (%)		NA
Low (0-1)	1682 (88.4)	
High (≥2)	220 (11.6)	
Bone metastases, No. (%)	n = 1595	
1-10	1117 (70.0)	195 (57.2)
>10	274 (17.2)	146 (42.8)
Unknown	204 (12.8)	0
Disease locations, No. (%)	n = 1883	n = 340
Bone only	1223 (64.3)	173 (50.7)
Bone and lymph nodes	313 (16.5)	143 (41.9)
Lymph nodes only	257 (13.5)	24 (7.0)
Visceral ± bone or lymph nodes	90 (4.7)	0
Liver	21 (1.1)	0
Lung	61 (3.2)	0
Brain	2 (0.1)	0
Visceral site(s) not reported	13 (0.7)	0
Laboratory parameters, median (IQR, Q1-Q3)		
ALP, U/L	82 (63-115) n = 1499	99 (75-146)
Hemoglobin, g/dL	12.8 (11.8-13.7) n = 1794	12.9 (11.7-13.7)
Lactate dehydrogenase, U/L	186 (159-218) n = 644	194 (172-224) n = 340
PSA, ng/mL	15.0 (5.2-46.1) n = 1884	51.7 (22.5-140.3)
Interval from diagnosis to first sipuleucel-T infusion, median (IQR, Q1-Q3), y	5.0 (2.3-9.4) n = 1599	7.1 (4.4-10.7)
Prior local cancer therapy, No. (%)		
No local therapy (systemic therapy only)	429 (22.6)	85 (24.9)
Radical prostatectomy alone	310 (16.3)	46 (13.5)
Radical prostatectomy + radiation	379 (19.9)	73 (21.4)
Radiation therapy alone (external beam/ brachytherapy)	564 (29.7)	112 (32.8)
Prior systemic cancer therapy, No. (%)		
Androgen-targeting therapy[a]	1881 (98.1)	279 (81.8)[b]
LHRH antagonist	382 (20.1)	—
LHRH agonist	1566 (82.3)	341 (100)[c]
Abiraterone	157 (8.3)	0
Enzalutamide	54 (2.8)	0
Chemotherapy		
Docetaxel	215 (11.3)	53 (15.5)
Cabazitaxel	32 (1.7)	0
Radium 223	1 (0.1)	0

Abbreviations: ALP, alkaline phosphatase; ECOG, Eastern Cooperative Oncology Group; IMPACT, Immunotherapy for Prostate Adenocarcinoma Treatment; IQR, interquartile range; LHRH, luteinizing hormone releasing hormone; max, maximum; min, minimum; NA, not applicable; PROCEED, PROVENGE Registry for the Observation, Collection, and Evaluation of Experience Data; PSA, prostate-specific antigen; Q1, first quartile; Q3, third quartile.
PROCEED was observational, so calculations were based on values from the number of patients for whom data were available.
[a]Excluded enzalutamide.
[b]Patients received complete androgen blockade treatment.
[c]Patients received an LHRH analogue.

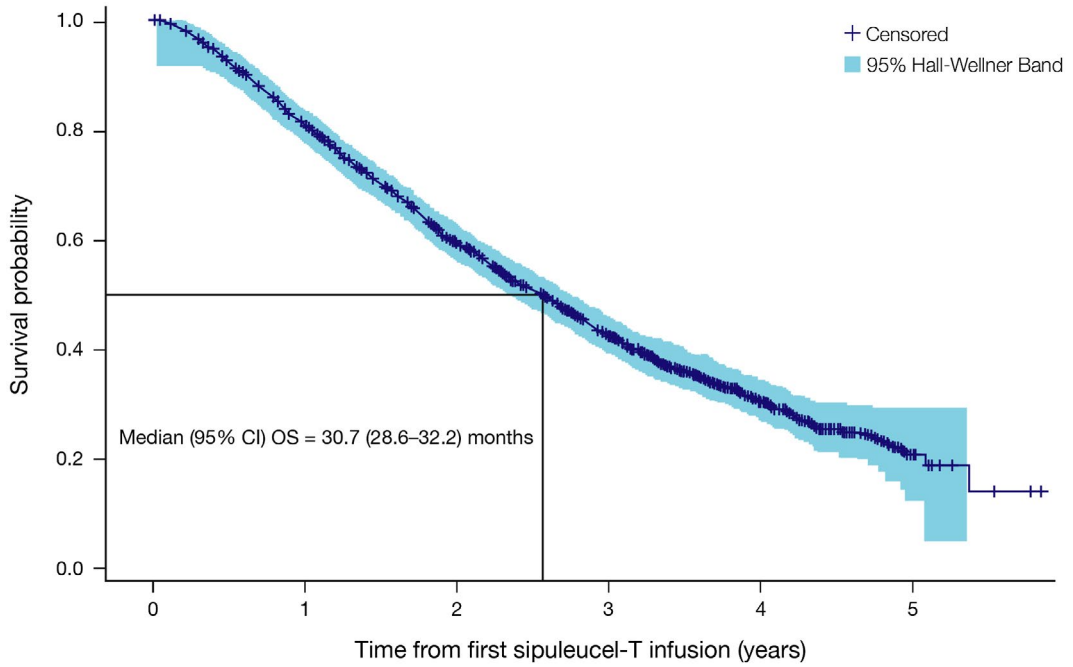


Figure 1. OS in PROCEED as a Kaplan-Meier plot with a 95% Hall-Wellner band. CI indicates confidence interval; OS, overall survival; PROCEED, PROVENGE Registry for the Observation, Collection, and Evaluation of Experience Data.

below .05 (Table 2): age, ethnicity, Eastern Cooperative Oncology Group performance status, time since diagnosis, PSA, alkaline phosphatase, hemoglobin, lymph node only metastases, prior abiraterone/enzalutamide, and prior docetaxel/cabazitaxel.

Cumulative sipuleucel-T product parameters (Supporting Table 3) per unit increase correlated with OS.

Safety

All-grade SAEs, regardless of causality, were reported in 260 patients (13.7%); the most common SAEs were disease progression (28 patients), cerebrovascular accident (16 patients), chills (13 patients), syncope (12 patients), and device-related infection (10 patients; Table 3). Seventy-four patients (3.9%) had 1 or more SAEs considered possibly or probably related to the study drug (all grades); the most common were chills (13 [0.7%]), cerebrovascular accident (9 [0.5%]), deep vein thrombosis (4 [0.2%]), device-related infection (4 [0.2%]), pulmonary embolism (4 [0.2%]), and pyrexia (4 [0.2%]). Grade 3 to 5 SAEs, regardless of causality, occurred in 175 patients (9.2%; Table 3). The incidence of grade 4 SAEs was 1.1% (n = 21). Fifty-two patients (2.7%) had grade 5 SAEs, and 22 deaths were due to disease progression. Central venous catheter–related SAEs were reported in 19 patients (1.0%); 13 were grade 3 or 4 with no grade 5 SAEs. Of these 19 patients, 2 and 5 had 1 and 2 sipuleucel-T infusions, respectively.

TABLE 2. Final Primary Multivariable Analysis of Overall Survival in PROCEED

Baseline Covariate	HR (95% CI)	P^a
Log PSA (ng/mL)	1.22 (1.16-1.27)	<.001
Hemoglobin, per g/dL increase	0.87 (0.83-0.91)	<.001
ECOG performance status, >0 vs 0	1.22 (1.05-1.42)	.009
Log ALP (U/L)	1.60 (1.42-1.81)	<.001
Age (y), >median vs ≤median	1.30 (1.12-1.50)	<.001
Race, white vs all others	1.64 (1.30-2.06)	<.001
Time since diagnosis (y), >median vs ≤median	0.72 (0.62-0.83)	<.001
Lymph node only metastases, yes vs no	0.79 (0.63-0.99)	.044
Visceral metastases, any vs none	1.30 (0.95-1.78)	.098
Prior docetaxel/cabazitaxel, yes vs no	1.54 (1.25-1.90)	<.001
Prior abiraterone/enzalutamide, yes vs no	1.53 (1.16-1.27)	<.001

Abbreviations: ALP, alkaline phosphatase; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; PROCEED, PROVENGE Registry for the Observation, Collection, and Evaluation of Experience Data; PSA, prostate-specific antigen.
[a]Multivariable Cox modeling.

The overall incidence of adjudicated CVEs (excluding TIAs) in PROCEED was 2.8% (n = 54), and the rate per 100 person-years was 1.2 (95% CI, 0.9-1.6; Supporting Table 4). In the SEER-Medicare data analyses of men with PC at diagnosis who were metastatic at

TABLE 3. Overall Summary of All-Grade SAEs and Grade 3 to 5 SAEs Occurring in 3 (0.2%) or More Patients (in the All-Grade List) Regardless of Causality (n = 1902) in PROCEED

	No. (%)	
SAE	All Grades	Grades 3-5
Any SAE	260 (13.7)	175 (9.2)
Disease progression	28 (1.5)	25 (1.3)
Cerebrovascular accident	16 (0.8)	11 (0.6)
Chills	13 (0.7)	0 (0)
Syncope	12 (0.6)	7 (0.4)
Device-related infection	10 (0.5)	7 (0.4)
Acute kidney injury	8 (0.4)	7 (0.4)
Deep vein thrombosis	8 (0.4)	2 (0.1)
Pulmonary embolism	8 (0.4)	7 (0.4)
Anemia	7 (0.4)	2 (0.1)
Dyspnea	7 (0.4)	6 (0.3)
Chest pain	6 (0.3)	2 (0.1)
Myocardial infarction	6 (0.3)	5 (0.3)
Pyrexia	6 (0.3)	2 (0.1)
Subdural hematoma	6 (0.3)	6 (0.3)
TIA	6 (0.3)	1 (0.1)
Cerebral hemorrhage	5 (0.3)	5 (0.3)
Pneumonia	5 (0.3)	3 (0.2)
Cerebral infarction	4 (0.2)	4 (0.2)
Congestive cardiac failure	4 (0.2)	3 (0.2)
Dehydration	4 (0.2)	3 (0.2)
Device-related sepsis	4 (0.2)	3 (0.2)
Intracranial hemorrhage	4 (0.2)	2 (0.1)
Nausea	4 (0.2)	1 (0.1)
Spinal cord compression	4 (0.2)	4 (0.2)
Vomiting	4 (0.2)	4 (0.2)
Asthenia	3 (0.2)	1 (0.1)
Atrial fibrillation	3 (0.2)	1 (0.1)
Back pain	3 (0.2)	2 (0.1)
Bacteremia	3 (0.2)	1 (0.1)
Confusional state	3 (0.2)	1 (0.1)
Constipation	3 (0.2)	2 (0.1)
Fall	3 (0.2)	3 (0.2)
Hematuria	3 (0.2)	1 (0.1)
Hypotension	3 (0.2)	2 (0.2)
Infusion-related reaction	3 (0.2)	2 (0.2)
Presyncope	3 (0.2)	1 (0.1)

Abbreviations: PROCEED, PROVENGE Registry for the Observation, Collection, and Evaluation of Experience Data; SAE, serious adverse event; TIA, transient ischemic attack.

follow-up and in a castrated state (n = 11,972), the CVE incidence (excluding TIAs) was 2.8%, and the rate per 100 person-years was 1.5 (95% CI, 1.4-1.7; Supporting Table 5).

Subgroup analyses of CVEs (excluding TIAs) showed higher CVE rates in older patients, African Americans, patients with more advanced PC, and those with preexisting conditions associated with CVEs (Supporting Table 6). Nine patients had a TIA (3 concurrent with another CVE and 6 in isolation). Thus, 60 PROCEED patients (3.2%) had CVEs, including TIAs, and the rate per 100 person-years was 1.3 (95% CI, 1.0-1.7; Supporting Table 4). The observed median time to a CVE (including TIAs) from the last sipuleucel-T infusion was

TABLE 4. Proportion of Patients Receiving an Overall Survival–Prolonging ACI After Sipuleucel-T Treatment

Posttreatment ACI	Safety Population (n = 1902)	Patients Who Died During PROCEED (n = 1255)
No. of posttreatment ACIs, No. (%)		
0	419 (22.0)	287 (22.9)
1	565 (29.7)	329 (26.2)
2	462 (24.3)	326 (26.0)
3	319 (16.8)	216 (17.2)
4	126 (6.6)	87 (6.9)
5	11 (0.6)	10 (0.8)
Specific posttreatment ACI, No. (%)		
Abiraterone	1036 (54.5)	663 (52.8)
Enzalutamide	831 (43.7)	514 (41.0)
Docetaxel	739 (38.9)	553 (44.1)
Cabazitaxel	309 (16.2)	236 (18.8)
Radium 223	90 (4.7)	61 (4.9)

Abbreviation: ACI, anticancer intervention; PROCEED, PROVENGE Registry for the Observation, Collection, and Evaluation of Experience Data.

321 days (10.5 months; interquartile range, 79-689 days or 2.6-22.6 months). For patients with a CVE (including TIAs), the number and percent of patients with CVE onset within ≤30, 31-60, 61-180, and >181 days of the most recent sipuleucel-T infusion were 10 (16.7%), 4 (6.7%), 9 (15.0%) and 37 (61.7%), respectively. No appreciable differences in the CVE ± TIA incidence or rate were observed between patients with or without a central venous catheter (Supporting Table 7).

Protocol-Specified, Exploratory Analysis: ACIs

Three hundred thirty-eight patients (17.8%) received an OS-prolonging ACI (abiraterone, enzalutamide, docetaxel, cabazitaxel, or radium 223) before sipuleucel-T. Approximately one-third of the patients (32.5%) did not receive any OS-prolonging ACI at 1 year, and 17.4% did not at 2 years after sipuleucel-T treatment. Of these patients, 9.5% and 7.4% had received an ACI before sipuleucel-T; thus, most of these patients had sipuleucel-T as first-line mCRPC therapy. Among patients in the lowest baseline PSA quartile (≤5.27 ng/mL), 44.1% and 25.8% did not receive an ACI at 1 and 2 years, respectively. Of these, 94.3% and 95.0% received sipuleucel-T before any other ACI.

During PROCEED, 1483 of all patients (78.0%) received 1 or more OS-prolonging ACIs, and 48.3% received 2 or more lines of treatment after sipuleucel-T (Table 4). The most commonly used OS-prolonging ACIs after sipuleucel-T treatment were abiraterone (1036 [54.5%]), enzalutamide (831 [43.7%]), and docetaxel

(739 [38.9%]; Table 4). Having sipuleucel-T as the only OS-prolonging treatment in PROCEED was reported in 22.0% of the patients (n = 419).

Similar patterns of ACI use were observed in patients who died during PROCEED (n = 1255), with 968 patients (77.1%) receiving 1 or more OS-prolonging ACIs and 50.9% receiving 2 or more lines of treatment after sipuleucel-T (Table 4). The most common OS-prolonging ACIs reported in those who died were abiraterone (52.8%), docetaxel (44.1%) and enzalutamide (41.0%; Table 4). Sipuleucel-T was the only OS-prolonging ACI prescribed in PROCEED for 22.9% of these patients (n = 287).

DISCUSSION

Since the conduct of the phase 3 IMPACT trial[1] with sipuleucel-T (2003-2007), mCRPC treatments[17-22] and guidelines[2-7] have rapidly evolved. The PROCEED study (2011-2017), which includes the largest mCRPC patient population treated with sipuleucel-T and prospectively followed in a real-world setting, offers interesting observations about patients with mCRPC, sipuleucel-T use, and the use of other ACIs since IMPACT. The baseline characteristics of PROCEED patients reveal clinical practice changes (Table 1). Although the median age was similar, the median baseline PSA level was much lower in PROCEED versus IMPACT (15.0 vs 51.7 ng/mL); this is noteworthy because a previous analysis of IMPACT showed a much greater OS benefit from sipuleucel-T versus a placebo in patients with lower baseline PSA levels.[8] Most PROCEED patients had a good performance status, although in comparison with IMPACT, the performance status was somewhat worse (likely because randomized clinical trials have more stringent eligibility criteria). The Gleason score was also higher in PROCEED. PROCEED enrolled a higher proportion of African American patients than IMPACT (11.6% vs 6.7%), and this is notable because this population is often underrepresented in clinical trials. Visceral metastases, an IMPACT exclusion criterion, were reported in 4.7% of PROCEED patients. Furthermore, PROCEED spanned a period of unprecedented progress in mCRPC management as 4 life-extending therapies became available: abiraterone acetate,[17,18] enzalutamide,[19,20] cabazitaxel,[21] and radium 223.[22] Thus, in PROCEED, the median OS (30.7 months) likely, in part, reflects use of these life-prolonging drugs with sipuleucel-T in contrast to the IMPACT (median OS, 25.8 months[1]) era, in addition to the use of sipuleucel-T in patients with lower PSA levels.

PROCEED provides further evidence of sipuleucel-T safety and tolerability in a real-world setting. Particularly in an elderly patient population, the safety profile of a treatment deserves careful consideration in decision making. Importantly, the SAE incidence in PROCEED was low and was comparable to that documented during IMPACT.[1] A previous analysis of pooled data from 4 phase 3 trials reported CVE rates (excluding TIAs) of 3.5% (sipuleucel-T) and 2.6% (placebo).[14] The causal relationship of sipuleucel-T with CVEs is unclear. Men with mCRPC are typically elderly with multiple comorbidities that increase the risk of cardiovascular events and CVEs. In PROCEED, a CVE rate of 2.8% was reported. Incidentally, the CVE rate was 2.8% in a SEER-Medicare database analysis with more than 10,000 patients with metastatic PC in a castrated state. Furthermore, subgroup analyses by baseline factors in PROCEED demonstrated that older patients and those with baseline CVE factors had higher rates of CVEs (Supporting Table 6), and this was consistent with published findings.[23-25] Moreover, although central venous catheter use (which varied greatly by site) for leukapheresis was high in PROCEED, overall, this practice did not increase CVE risk (Supporting Table 7).

PROCEED also offers confirmation of correlative findings noted in prior phase 3 studies. Patients in the lowest baseline PSA quartile (PSA ≤ 5.27 ng/mL) had significantly longer OS (median survival, 47.7 months) than those in higher PSA quartiles. Similar findings were seen in the post hoc analysis of IMPACT, which demonstrated a greater OS benefit in lower baseline PSA quartiles versus higher baseline PSA quartiles and also suggested that sipuleucel-T was superior to a placebo in each quartile.[8] Likewise, similar correlations with immune parameters and OS were seen in both PROCEED and IMPACT; in vitro indicators of immune activation and product potency (cumulative APC activation, APC count, and total nucleated cell count in the product) were significantly correlated with OS (Supporting Table 3).[26,27]

PROCEED also exhibited 10 baseline characteristics that were independent predictors of OS in PROCEED (Table 2). The examined covariates were selected on the basis of those previously observed to be clinically and statistically relevant in this population. Our findings, though broadly consistent with the Halabi model,[28] also differ in terms of which significant predictors were identified, potentially because of the treatment being received (chemotherapy in the population used for

the Halabi nomogram and sipuleucel-T for the current study), the data coming from a clinical trial versus a registry, the time periods during which the various studies informing these analyses were conducted and the changes in available therapies and PSA levels guiding treatment, and so on. One notable observation is the emergence of race as a statistically significant predictor, and this potentially reflects the relatively high enrollment of African Americans in PROCEED (12%). Further research is warranted to explore these findings.

Another notable finding in PROCEED is that a substantial number of patients experienced a long interval between sipuleucel-T and subsequent therapy with abiraterone, enzalutamide, docetaxel, cabazitaxel, or radium 223. Approximately one-third and one-sixth of the patients had not received any of these agents 1 and 2 years, respectively, after sipuleucel-T. For most of these patients, sipuleucel-T was their first OS-prolonging mCRPC therapy; having a long treatment-free interval after sipuleucel-T may reflect patient selection as well as the clinical benefit of sipuleucel-T. Interestingly, 22% of the overall PROCEED population received sipuleucel-T as their only OS-prolonging treatment for mCRPC. The reasons for this are unclear. However, the long median time to death from PC of 42.7 months observed provides further evidence for the early use of sipuleucel-T for mCRPC followed by other ACIs, as recommended by the National Comprehensive Cancer Network and other guidelines.[2-4,7]

PROCEED has several limitations. Although OS was prospectively determined, there was no comparator group, so a survival benefit could not be determined. Nonetheless, this observation gives an accurate picture of expected OS with sipuleucel-T plus other life-prolonging drugs that were not available when IMPACT was conducted. Similar reasoning applies to SAE and CVE risk in that there was no placebo arm; hence, the results are descriptive.

PROCEED provides a real-world portrait of the safety profile of sipuleucel-T and defines the expected OS after sipuleucel-T in patients with mCRPC in the modern era of 5 additional life-prolonging agents. This information may be useful in powering future combination trials with sipuleucel-T, and studying the sequencing of therapies in this large population may shed light on optimal treatment approaches.

FUNDING SUPPORT

PROCEED was funded by Dendreon Pharmaceuticals LLC. Work conducted at Memorial Sloan Kettering Cancer Center (New York, New York) was funded in part through National Institutes of Health/National Cancer Institute Cancer Center Support Grant P30 CA008748. Medical writing assistance, in the form of developing the draft outline and manuscript first draft in consultation with the authors, revising draft versions of this article, assembling tables and figures, collating author comments, copyediting, fact checking, referencing, graphic services, and submission, was provided by Jackie Phillipson, PhD, of Zoetic Science (Macclesfield, United Kingdom) and was funded by Dendreon Pharmaceuticals LLC. Additional medical editing assistance was provided by Helen M. Wilfehrt, PhD, CMPP, of Dendreon Pharmaceuticals LLC.

CONFLICT OF INTEREST DISCLOSURES

Celestia S. Higano has served in an advisory role for Aptevo, Asana, Astellas, Bayer, Blue Earth Diagnostics, Churchill Pharma, Clovis Oncology, Dendreon, Endocyte, Ferring, Medivation, Orion Corporation, and Pfizer; she has also participated in sponsored research for Aptevo, Bayer, Aragon Pharma, Astellas, AstraZeneca, Dendreon, Genentech, Hoffman-LaRoche, Medivation, Sanofi, and Pfizer, and her spouse was in a leadership role for CTI Biopharma. Andrew J. Armstrong has received grants and personal fees from Dendreon, Pfizer/Astellas, Janssen, Bayer, and Sanofi-Aventis during this study as well as grants from Novartis, Gilead, Bristol-Myers Squibb, and Genentech/Roche outside the submitted work. A. Oliver Sartor has served as a consultant for and received personal fees from Advanced Accelerator Applications, Astellas, AstraZeneca, Bavarian-Nordic, Bayer, Bellicum, Blue Earth Diagnostics, Celgene, Constellation, Dendreon, EMD Serono, Endocyte, Johnson & Johnson, Bristol-Myers Squibb, Myovant, Pfizer, Progenics, Sanofi, Teva, and Hinova during this study; he has also received grants from AstraZeneca, Bayer, Constellation, Dendreon, Endocyte, Johnson & Johnson, Bristol-Myers Squibb, Progenics, Sanofi, Innocrin, Invitae, Merck, Roche, and Sotio. Philip W. Kantoff has received personal fees from Astellas, Bayer, Bellicum, BIND Biosciences, Bavarian Nordic Immunotherapies, DRGT, Genentech/Roche, Ipsen Pharmaceuticals, Janssen, Metamark, Merck, Millennium/Prometrika, MTG, Omnitura, OncoCell MDx, OncoGenex, Progenity, Sanofi, Tarveda Pharmaceuticals, Thermo Fisher, GE Healthcare, Context Therapeutics, New England Research Institutes, SEER Biosciences, and Placon; he also has investment interests in DRGT, Tarveda Pharmaceuticals, Context Therapeutics, SEER Biosciences, and Placon. Christopher M. Pieczonka has received personal fees as a consultant for Dendreon, Bayer, Janssen, and Pfizer and as an investigator for Dendreon, Bayer, Janssen, Pfizer, Merck, AstraZeneca, Taiho, Innocrin, and Myovant outside the submitted work. David F. Penson has received personal fees from Dendreon and Janssen as well as a grant from the Vanderbilt University Research Center. Neal D. Shore has served as a consultant for and received personal fees from Ferring, Bayer, Amgen, Janssen, Dendreon, Tolmar, Astellas, Pfizer, AstraZeneca, Genentech/Roche, Myovant Sciences, Merck, Bristol Meyers Squibb, and Nymox outside the submitted work. Raoul S. Concepcion has served in an advisory role for Dendreon and received personal fees outside the submitted work. David I. Quinn has been involved in payments to the University of Southern California for trial conduct with Dendreon; he has also acted as an advisor for and received personal fees from Dendreon, Bayer, Janssen, Pfizer, Astellas, Genzyme, Clovis, and AstraZeneca. Vahan Kassabian has served as a consultant or speaker for Dendreon, Amgen, Astellas, Pfizer, Janssen, Bayer, UroGPO, Tolmar, and Genomic Health outside the submitted work and is a shareholder of UroGPO. Matt Harmon reports stock ownership in Amgen. Robert C. Tyler has been an employee of Janssen, Dendreon, Medivation, Pfizer, and Innocrin. Nancy N. Chang was a full-time employee of Dendreon at the time of the analyses and drafting of this manuscript. Hong Tang was a full-time employee of Dendreon at the time of the analyses and drafting of the manuscript; is a nonexecutive director of OnQuality Pharmaceuticals; and owns stock in BeiGene, Nektar, Sangamo Therapeutics, Tesaro, Verastem, Editas Medicine, and CVS Health Corporation. Matthew R. Cooperberg has received personal fees from Dendreon in relation to a PROCEED trial steering committee and has served in an advisory or consultancy role for Bayer, MDx Health, and Myriad Genetics; he has also participated in a registry steering committee for Astellas. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

Celestia S. Higano: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, visualization, writing–original draft, and writing–review and editing. **Andrew J. Armstrong:** Conceptualization, investigation, methodology, project administration, resources, supervision, writing–original draft, and writing–review and editing. **A. Oliver Sartor:** Conceptualization, data curation, formal analysis, investigation, methodology, supervision, writing–original draft, and writing–review and editing. **Nicholas J. Vogelzang:** Investigation, writing–original draft, and writing–review and editing. **Philip W. Kantoff:** Conceptualization, investigation, and writing–review and editing. **David G. McLeod:** Writing–original draft and writing–review and editing. **Christopher M. Pieczonka:** Investigation and writing–review and editing. **David F. Penson:** Investigation, methodology, and writing–review and editing. **Neal D. Shore:** Formal analysis, investigation, and writing–review and editing. **Jeffrey Vacirca:** Data curation, investigation, project administration, resources, software, supervision, validation, and visualization. **Raoul S. Concepcion:** Investigation and writing–review and editing. **Ronald F. Tutrone:** Data curation, investigation, and writing–review and editing. **Luke T. Nordquist:** Investigation and writing–review and editing. **David I. Quinn:** Investigation and writing–review and editing. **Vahan Kassabian:** Investigation, validation, visualization, and writing–review and editing. **Mark C. Scholz:** Investigation, supervision, and writing–review and editing. **Matt Harmon:** Data curation, methodology, software, visualization, and writing–review and editing. **Robert C. Tyler:** Conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, and writing–review and editing. **Nancy N. Chang:** Visualization, writing–original draft, and writing–review and editing. **Hong Tang:** Funding acquisition, resources, supervision, and writing–review and editing. **Matthew R. Cooperberg:** Conceptualization, methodology, supervision, visualization, and writing–review and editing.

REFERENCES

1. Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med*. 2010;363:411-422.
2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Prostate Cancer: Version 1.2018. Published February 14, 2018. Accessed November 21, 2018. https://www.nccn.org/professionals/physician_gls/default.aspx
3. McNeel DG, Bander NH, Beer TM, et al. The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of prostate carcinoma. *J Immunother Cancer*. 2016;4:92.
4. Cookson MS, Roth BJ, Dahm P, et al. Castration-resistant prostate cancer: AUA guidelines 2018. Accessed December 11, 2018. http://www.auanet.org/guidelines/prostate-cancer-castration-resistant-(2013-amended-2018)
5. Basch E, Loblaw DA, Oliver TK, et al. Systemic therapy in men with metastatic castration-resistant prostate cancer: American Society of Clinical Oncology and Cancer Care Ontario clinical practice guideline. *J Clin Oncol*. 2014;32:3436-3448.
6. Parker C, Gillessen S, Heidenreich A, Horwich A; ESMO Guidelines Committee. Cancer of the prostate: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2015;26(suppl 5):v69-v77.
7. Crawford ED, Petrylak DP, Shore N, et al. The role of therapeutic layering in optimizing treatment for patients with castration-resistant prostate cancer (Prostate Cancer Radiographic Assessments for Detection of Advanced Recurrence II). *Urology*. 2017;104:150-159.
8. Schellhammer PF, Chodak G, Whitmore JB, Sims R, Frohlich MW, Kantoff PW. Lower baseline prostate-specific antigen is associated with a greater overall survival benefit from sipuleucel-T in the Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT) trial. *Urology*. 2013;81:1297-1302.
9. Beer TM, Bernstein GT, Corman JM, et al. Randomized trial of autologous cellular immunotherapy with sipuleucel-T in androgen-dependent prostate cancer. *Clin Cancer Res*. 2011;17:4558-4567.
10. Antonarakis ES, Kibel AS, Yu EY, et al. Sequencing of sipuleucel-T and androgen deprivation therapy in men with hormone sensitive biochemically recurrent prostate cancer: a phase II randomized trial. *Clin Cancer Res*. 2017;23:2451-2459.
11. Small EJ, Lance RS, Gardner TA, et al. A randomized phase II trial of sipuleucel-T with concurrent versus sequential abiraterone acetate plus prednisone in metastatic castration-resistant prostate cancer. *Clin Cancer Res*. 2015;21:3862-3869.
12. Small EJ, Schellhammer PF, Higano CS, et al. Placebo-controlled phase III trial of immunologic therapy with sipuleucel-T (APC8015) in patients with metastatic, asymptomatic hormone refractory prostate cancer. *J Clin Oncol*. 2006;24:3089-3094.
13. Higano CS, Schellhammer PF, Small EJ, et al. Integrated data from 2 randomized, double-blind, placebo-controlled, phase 3 trials of active cellular immunotherapy with sipuleucel-T in advanced prostate cancer. *Cancer*. 2009;115:3670-3679.
14. PROVENGE® (sipuleucel-T) prescribing information. Published July 2017. Accessed December 11, 2018. http://www.provengehcp.com/Portals/5/Provenge-PI.pdf
15. Easton JD, Saver JL, Albers GW, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. *Stroke*. 2009;40:2276-2293.
16. Ulm K. A simple method to calculate the confidence interval of a standardized mortality ratio (SMR). *Am J Epidemiol*. 1990;131:373-375.
17. Fizazi K, Scher HI, Molina A, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol*. 2012;13:983-992.
18. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med*. 2013;368:138-148.
19. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med*. 2012;367:1187-1197.
20. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med*. 2014;371:424-433.
21. de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet*. 2010;376:1147-1154.
22. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med*. 2013;369:213-223.
23. Lim JS, Kwon HM. Risk of "silent stroke" in patients older than 60 years: risk assessment and clinical perspectives. *Clin Interv Aging*. 2010;5:239-251.
24. Smithard DG. Stroke in frail older people. *Geriatrics (Basel)*. 2017;2:24. doi:10.3390/geriatrics2030024
25. Benjamin EJ, Virani SS, Callaway CW, et al. Heart disease and stroke statistics—2018 update: a report from the American Heart Association. *Circulation*. 2018;137:e67-e492.
26. Sheikh NA, Jones LA. CD54 is a surrogate marker of antigen presenting cell activation. *Cancer Immunol Immunother*. 2008;57:1381-1390.
27. Sheikh NA, Petrylak D, Kantoff PW, et al. Sipuleucel-T immune parameters correlate with survival: an analysis of the randomized phase 3 clinical trials in men with castration-resistant prostate cancer. *Cancer Immunol Immunother*. 2013;62:137-147.
28. Halabi S, Lin CY, Kelly WK, et al. Updated prognostic model for predicting overall survival in first-line chemotherapy for patients with metastatic castration-resistant prostate cancer. *J Clin Oncol*. 2014;32:671-677.

original reports

Phase I Study of DSTP3086S, an Antibody-Drug Conjugate Targeting Six-Transmembrane Epithelial Antigen of Prostate 1, in Metastatic Castration-Resistant Prostate Cancer

Daniel C. Danila, MD[1]; Russell Z. Szmulewitz, MD[2]; Ulka Vaishampayan, MD[3]; Celestia S. Higano, MD[4]; Ari D. Baron, MD[5]; Houston N. Gilbert, PhD[6]; Flavia Brunstein, MD, PhD[6]; Marija Milojic-Blair[6]; Bei Wang, MS[6]; Omar Kabbarah, PhD[6]; Michael Mamounas, PhD[6]; Bernard M. Fine, MD, PhD[6]; Daniel J. Maslyar, MD[6]; Alexander Ungewickell, MD, PhD[6]; and Howard I. Scher, MD[1]

abstract

PURPOSE Six-transmembrane epithelial antigen of the prostate 1 (STEAP1) is highly expressed in prostate cancers. DSTP3086S is a humanized immunoglobulin G1 anti-STEAP1 monoclonal antibody linked to the potent antimitotic agent monomethyl auristatin E. This study evaluated the safety and activity of DSTP3086S in patients with metastatic castration-resistant prostate cancer.

METHODS Patients were enrolled in a 3 + 3 dose escalation study to evaluate DSTP3086S (0.3 to 2.8 mg/kg intravenously) given once every 3 weeks followed by cohort expansion at the recommended phase II dose or weekly (0.8 to 1.0 mg/kg).

RESULTS Seventy-seven patients were given DSTP3086S once every 3 weeks, and seven were treated weekly. Two patients in the once-every-3-weeks dose escalation had dose-limiting grade 3 transaminitis. Grade 3 hyperglycemia and grade 4 hypophosphatemia were dose-limiting toxicities in one patient treated at 1.0 mg/kg weekly. Initial cohort expansion evaluated dosing at 2.8 mg/kg once every 3 weeks (n = 10), but frequent dose reductions led to testing of 2.4 mg/kg (n = 39) in the expansion phase. Common related adverse events (> 20%) across doses (once every 3 weeks) were fatigue, peripheral neuropathy, nausea, constipation, anorexia, diarrhea, and vomiting. DSTP3086S pharmacokinetics were linear. Among 62 patients who received > 2 mg/kg DSTP3086S once every 3 weeks, 11 (18%) demonstrated a ≥ 50% decline in prostate-specific antigen; two (6%) of 36 with measurable disease at baseline achieved a radiographic partial response; and of 27 patients with informative unfavorable baseline circulating tumor cells ≥ 5/7.5 mL of blood, 16 (59%) showed conversions to favorable circulating tumor cells < 5. No prostate-specific antigen or RECIST responses were seen with weekly dosing.

CONCLUSION DSTP3086S has acceptable safety at the recommended phase II dose level of 2.4 mg/kg once every 3 weeks. Antitumor activity at doses between 2.25 and 2.8 mg/kg once every 3 weeks supports the potential benefit of treating STEAP1-expressing metastatic castration-resistant prostate cancer with an STEAP1-targeting antibody-drug conjugate.

J Clin Oncol 37:3518-3527. © 2019 by American Society of Clinical Oncology

ASSOCIATED CONTENT

Data Supplements

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on October 3, 2019 and published at jco.org on November 5, 2019: DOI https://doi.org/10.1200/JCO.19.00646

Clinical trials information: NCT01283373.

INTRODUCTION

Treatment options with clinical benefit for metastatic castration-resistant prostate cancer (mCRPC) have expanded significantly with the addition of abiraterone,[1,2] enzalutamide,[3] radium-223,[4] and cabazitaxel.[5] The long-term benefit for these agents, however, remains limited and is associated with significant toxicity.[2,3,6,7] Needed are well-tolerated, targeted treatments with improved clinical benefit for patients whose tumors express the therapeutic target.

Six-transmembrane epithelial antigen of the prostate 1 (STEAP1) is a multitransmembrane protein believed to act as an ion channel or transporter protein.[8] As a cell surface protein frequently expressed in prostate cancer, with limited expression in nonprostate tissues,[9-11] STEAP1 is an ideal candidate for antibody-derived therapies in patients with mCRPC.

DSTP3086S is an antibody-drug conjugate (ADC) that contains the humanized immunoglobulin G1 anti-STEAP1 monoclonal antibody MSTP2109A linked through a protease labile linker, maleimidocaproyl-valine-citrulline *p*-aminobenzyloxycarbonyl, to a potent antimitotic agent, monomethyl auristatin E (MMAE). After antigen-specific binding of the ADC, the complex

is internalized, and MMAE is released intracellularly, resulting in inhibition of cell division and cell death.[12-14] Nonclinical efficacy studies in prostate cancer xenografts provided a rationale for investigating DSTP3086S in patients with mCRPC.[11]

METHODS

Study Design and Patient Selection

This phase I, multicenter, open-label, 3 + 3, dose-escalation study was designed to evaluate the safety and identify the recommended phase II dose (RP2D) of DSTP3086S in patients with mCRPC. Secondary and exploratory objectives included assessment of the antitumor activity of DSTP3086S in association with STEAP1 expression and of the predictive value of measuring circulating tumor cell (CTC) counts during treatment. The study protocol was approved by institutional review boards before patient recruitment and conducted in accordance with International Conference on Harmonization E6 Guidelines for Good Clinical Practice. Each patient provided signed informed consent before study enrollment.

Study eligibility criteria, including paraffin-embedded tissue screening for STEAP1 expression, are described in the Data Supplement (online only). In the initial dose-escalation stage, patients received intravenous DSTP3086S (supplied by Genentech, South San Francisco, CA) at 0.3 to 2.8 mg/kg once every 3 weeks, with dosing calculated by weight and eventually capped during the 2.4 mg/kg expansion for patients with a body mass index > 35 kg/m^2 because of excess toxicity seen in morbidly obese patients at higher dose levels. After completing the once-every-3-weeks dose escalation, a weekly schedule was evaluated at 0.8 and 1 mg/kg.

The RP2D was determined on the basis of cumulative safety data obtained at the time of cohort expansion. Dose-expansion cohorts were enrolled at RP2D to further characterize safety, tolerability, pharmacokinetics (PK) variability, and signals of clinical activity in 49 patients with STEAP1-expressing tumors (immunohistochemistry [IHC] 3+, predominantly strong staining; IHC 2+, predominantly moderate staining; IHC 1+, predominantly weak staining; IHC 0, very weak or no staining in $> 90\%$ of tumor cells). Patients enrolled in the expansion phase were required to have an STEAP1 IHC score of 2+ or 3+ in an archival or a pretreatment tissue biopsy specimen. A second expansion cohort enrolled chemotherapy-naïve patients who had progressed on abiraterone and/or enzalutamide and received daily prednisone concurrent with DSTP3086S.

Safety Assessment

Safety was assessed on the basis of reports of adverse events (AEs) and included clinical laboratory testing, vital signs, physical examinations, and ECG. Patients were assessed for AEs at each study visit and as necessary throughout the study. AEs were graded in severity according to the National Cancer Institute CTCAE (version 4.0). Dose-limiting toxicities (DLTs) were defined as grade ≥ 3 nonhematologic or grade ≥ 4 hematologic toxicities attributed to treatment that occurred in the first cycle (for exceptions and additional details, see the Data Supplement). Patients with DLTs could continue treatment at a lower dose if toxicities resolved to grade < 2. The maximum tolerated dose was defined as the highest dose at which zero or one of six patients experienced a DLT. PK and immunogenicity assessments are described in the Data Supplement.

Clinical Activity

Preliminary efficacy measures included post-therapy prostate-specific antigen (PSA) changes shown by waterfall plots, disease progression according to Prostate Cancer Clinical Trials Working Group criteria,[15] and radiographic response according to RECIST version 1.0.[16] Per the Prostate Cancer Clinical Trials Working Group, treatment beyond PSA progression in the absence of radiographic or clinically progressive disease was allowed.[15] Exploratory measures of activity included changes in CTC counts from unfavorable ≥ 5 cells to favorable ≤ 4 cells/7.5 mL of blood per US Food and Drug Administration clearance for CellSearch (Menarini Silicon Biosystems, Huntingdon Valley, PA).[17-22] STEAP1 IHC was performed as described in the Data Supplement.

Statistical Analysis

This study was designed to obtain preliminary safety, PK, and activity information in the treated populations. As such, the sample sizes in the various dose-escalation and dose-expansion cohorts did not reflect explicit, formal power and type I error considerations. Rather, sample sizes were based on an estimation framework either for the ability to identify AEs with various assumed underlying prevalence or for their ability to initially assess antitumor activity and evaluate benefits and risks in this patient population. For safety analysis, all patients who received DSTP3086S were included. Patients were considered for evaluation for response if the baseline PSA was detectable, they had measurable disease as assessed by computed tomography/magnetic resonance imaging by RECIST version 1.0, or they had baseline CTCs ≥ 5/7.5 mL of blood.

RESULTS

Patient baseline characteristics for each schedule are listed in Table 1. A total of 84 patients were enrolled, including 77 on the once-every-3-weeks dose schedule of whom 28 were enrolled in the dose escalation (0.3 to 2.8 mg/kg), 10 in an initial expansion at 2.8 mg/kg, and 39 at 2.4 mg/kg in two expansion cohorts. The median number of DSTP3086S dose administrations in the once-every-3-weeks cohort was four (range, one to 25). AEs led to dose delays in 29 patients (38%), dose reductions in 12 (16%), and dose discontinuations in 17 (22%). Peripheral neuropathy was the most

TABLE 1. Patient Demographics and Disease Characteristics

Characteristic	DSTP3086S Cohort, No. (%)	
	Once Every 3 Weeks	Weekly
No. of patients	77	7
Median age, years (range)	68 (43-88)	67 (47-75)
ECOG performance status		
0	23 (30)	3 (43)
1	53 (69)	3 (43)
2	1 (1)	1 (14)
Sites of metastatic disease		
Bone	69 (90)	5 (71)
Bone only	5 (7)	0 (0)
Soft tissue	50 (65)	6 (86)
Lung	15 (20)	1 (14)
Liver	11 (14)	2 (29)
Lymph node	42 (55)	6 (86)
Prior systemic therapies (selected)		
Docetaxel	43 (56)	3 (43)
Cabazitaxel	8 (10)	1 (14)
Abiraterone	52 (68)	6 (86)
Enzalutamide	35 (45)	3 (43)
Median baseline prognostic factors (range)		
PSA, ng/mL	89 (0.4-8,471)	21 (0.3-274)
Hgb, g/dL	12 (8-15)	11 (10-13)
Alkaline phosphatase, U/L	134 (43-668)	98 (53-277)
LDH, U/L	236 (117-2,023)	212 (192-631)
Albumin, g/dL	4.1 (1.9-4.7)	4.1 (3.2-4.6)
Baseline CTCs/7.5 mL of blood		
Median (range)	6 (0-446)	1 (0-908)
≥ 5	38 (49)	2 (29)

Abbreviations: CTC, circulating tumor cell; ECOG, Eastern Cooperative Oncology Group; Hgb, hemoglobin B, LDH, lactate dehydrogenase; PSA, prostate-specific antigen.

common AE that led to treatment discontinuation. Dose reductions occurred after one to nine cycles of DSTP3086S treatment in the three highest dose cohorts, including 50% of patients at 2.8 mg/kg (Fig 1).

Of the seven patients enrolled in the weekly dose schedule, four were enrolled at 0.8 mg/kg, and three were enrolled at 1.0 mg/kg; no expansions were performed in the weekly schedule. The median number of DSTP3086S dose administrations in the weekly cohort was seven (range, one to 32); one patient (14%) had a dose reduction, three patients (43%) had dose delays, and one patient (14%) discontinued treatment because of AEs.

Safety

In the once-every-3-weeks dose escalation, DLTs included grade 3 transaminitis in one patient each at 2.25 mg/kg and 2.8 mg/kg. The maximum tolerated dose was not reached, and the RP2D for DSTP3086S was determined to be 2.4 mg/kg once-every 3 weeks on the basis of tolerability after an initial expansion at 2.8 mg/kg once every 3 weeks was deemed not tolerable and required frequent dose reductions (Fig 1).

The most common treatment-related AEs, defined as having occurred in > 20% patients (15 of 77) over all once-every-3-week dose levels, were fatigue (56%), peripheral neuropathy (51%), nausea (38%), constipation (35%), decreased appetite (34%), diarrhea (26%), and vomiting (25%). Table 2 lists related AEs that occurred in ≥ 10% patients in the once-every-3-weeks dose cohort. AEs reported at a maximum intensity of grade ≥ 3 in ≥ 5% of patients over all once-every-3-weeks dose levels (regardless of attribution to study drug) were hyperglycemia (eight

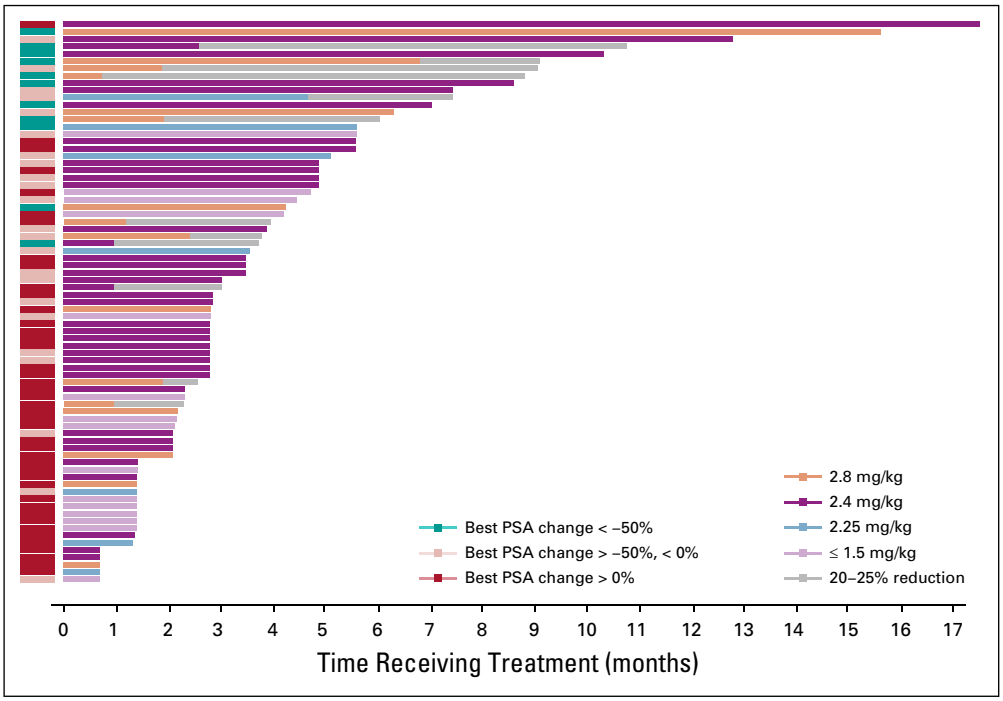


FIG 1. Time on treatment by dosing cohort and corresponding best prostate-specific antigen (PSA) changes in the once-every-3-weeks dose cohort. Dose modifications are represented by changes in color.

patients; 10% [includes one event of blood glucose increased]); anemia and fatigue (five patients each; 7%); and back pain, neutropenia, and pulmonary embolism (four patients each; 5%). Treatment-emergent grade ≥ 3 AEs reported in at least two patients are listed in the Data Supplement. Grade ≥ 3 AEs that the investigator considered to be related to the study drug were reported in 34% of patients (26 of 77) on the once-every-3-weeks dose

TABLE 2. Most Common Related Adverse Events (Any and Grade 3/4) That Occurred in 10% or More Patients in the Once-Every-3-Weeks Dose Cohort

	Grade, No. (%)									
	DSTP3086S									
	≤ 1.5 mg/kg (n = 15)		2.25 mg/kg (n = 7)		2.4 mg/kg (n = 39)		2.8 mg/kg (n = 16)		Total (N = 77)	
Adverse Event	Any	3/4	Any	3/4	Any	3/4	Any	3/4	Any	3/4
Overall	10 (67)	2 (13)	5 (71)	3 (43)	38 (97)	9 (23)	16 (100)	10 (63)	69 (90)	24 (31)
Fatigue	4 (27)	—	2 (29)	—	25 (64)	—	12 (75)	3 (19)	43 (56)	3 (4)
Peripheral neuropathy*	1 (7)	—	2 (29)	1 (14)	26 (67)	2 (5)	10 (63)	—	39 (51)	3 (4)
Nausea	3 (20)	1 (7)	1 (14)	—	15 (39)	—	10 (63)	—	29 (38)	1 (1)
Constipation	3 (20)	—	2 (29)	—	14 (36)	—	8 (50)	1 (6)	27 (35)	1 (1)
Appetite decreased	2 (13)	—	1 (14)	—	16 (41)	—	7 (44)	—	26 (34)	—
Diarrhea	2 (13)	—	2 (29)	—	10 (26)	—	6 (38)	—	20 (26)	—
Vomiting	2 (13)	—	—	—	10 (26)	—	7 (44)	—	19 (25)	—
Dyspnea	—	—	1 (14)	—	8 (21)	—	5 (31)	1 (6)	14 (18)	1 (1)
ALT increased	1 (7)	—	—	—	9 (23)	2 (5)	1 (6)	—	11 (14)	2 (3)
AST increased	1 (7)	—	1 (14)	1 (14)	6 (15)	—	1 (6)	—	9 (12)	1 (1)
Pain in extremity	—	—	2 (29)	—	5 (13)	—	1 (6)	1 (6)	8 (10)	1 (1)

NOTE. None of the most common related adverse events that occurred in ≥ 10% of patients were grade 5. See the Safety section for a description of related grade 5 adverse events and the Data Supplement for a complete list of grade ≥ 3–related adverse events in the once-every-3-weeks dose cohort.

*Includes the Medical Dictionary of Regulatory Activities preferred terms peripheral sensory neuropathy, peripheral motor neuropathy, neuropathy peripheral and muscular weakness, hypoesthesia, gait disturbance, and paresthesia and peripheral sensorimotor neuropathy.

schedule (Data Supplement). The most frequently reported grade ≥ 3–related AE was neutropenia (four patients; 5%).

Serious AEs are listed in the Data Supplement. Drug-related serious AEs occurred in nine patients at the once-every-3-weeks dose levels, including two fatal events: one as a result of sepsis (at 2.25 mg/kg) and one as a result of sepsis and respiratory failure after initial hospitalization for hyperglycemia (at 2.4 mg/kg). Thirteen patients (17%) had a glucose value consistent with grade ≥ 3 hyperglycemia while in the study, with eight (10%) of the 13 reported as grade ≥ 3 AEs. Of note, fasting glucose levels, which are used when making the CTCAE determinations, were not required for this study.

In the weekly cohort, one patient treated with 1.0 mg/kg developed grade 3 hyperglycemia and grade 4 hypophosphatemia, which were considered DLTs. AEs commonly experienced by the patients who received weekly treatment are listed in the Data Supplement. Treatment-emergent grade ≥ 3 AEs for patients on the weekly dose schedule are listed in the Data Supplement. One of seven patients developed nonfatal serious AEs that included dehydration, hyperglycemia, hypomagnesemia, and hypophosphatemia that led to treatment discontinuation.

Peripheral neuropathy–related AEs, regardless of attribution to study drug (identified using the broad Standardized Medical Dictionary for Regulatory Activities Queries for peripheral neuropathy), were reported in 46 patients (60%) on the once-every-3-weeks dose schedule after a median of 2.8 months of treatment. For patients on the weekly dose schedule, peripheral neuropathy–related AEs were reported in two (29%). Overall, grade 3 peripheral sensory neuropathy was reported in three patients, with one also having grade 3 peripheral motor neuropathy. Overall, nine patients (12%) on the once-every-3-weeks dose schedule and none of the weekly cohort discontinued DSTP3086S treatment because of a peripheral neuropathy–related AE. The majority of peripheral neuropathy AEs were reported as ongoing at the end of the reporting period for the study, which ended 30 days after a patient's last dose.

TABLE 3. Pharmacokinetic Parameters for DSTP3086S Tab, acMMAE, and Unconjugated MMAE Analytes in Cycle 1 at 2.4 mg/kg

Parameter	DSTP3086S 2.4 mg/kg Once Every 3 Weeks (n = 36), Mean (% CV)
C_{max}	
Tab, μg/mL	56 (23)
acMMAE, ng/mL	879 (20)
Unconjugated MMAE, ng/mL	5.8 (55)
$AUC_{0-\infty}$	
Tab, day × μg/mL	313 (26)
acMMAE, day × ng/mL	2,423 (20)
Unconjugated MMAE, day × ng/mL	44 (50)
CL	
Tab, mL/day/kg	8.3 (32)
acMMAE, mL/day/kg	17.5 (23)

Abbreviations: acMMAE, antibody-conjugated monomethyl auristatin E; AUC, area under the curve; CL, clearance; C_{max}, maximum concentration; CV, coefficient of variation; MMAE, monomethyl auristatin E; Tab, total antibody.

PK and Immunogenicity Assessments

Linear PK (0.3 to 2.8 mg/kg) were observed for total antibody (Tab) and antibody-conjugated MMAE (acMMAE [RP2D of 2.4 mg/kg listed in Table 3]). For the once-every-3-weeks regimen, the mean acMMAE maximum concentrations occurred immediately after the infusion, increased with dose, and ranged from 94 to 993 ng/mL. The acMMAE PK showed a multi-exponential decline, with half-life values ranging from 4.6 to 6.4 days. The acMMAE PK was similar to the Tab, with a trend of faster clearance for acMMAE than for the Tab analyte. Unconjugated MMAE levels increased with DSTP3086S dose, and systemic exposure of unconjugated MMAE was consistently low across all time points (approximately 100-fold less than the exposure to acMMAE) and exhibited formation-rate-limited kinetics (Data Supplement). Minimal accumulation was observed for the acMMAE, Tab, and unconjugated MMAE analytes upon repeated dosing on the once-every-3-weeks schedule, and steady state seemed to be reached within the first dose in cycle 1.

For the tested weekly regimen of 0.8 and 1.0 mg/kg, dose-proportional maximum concentrations and areas under the curve were observed. On the basis of the limited weekly dosing data, faster clearance was observed for the weekly regimen compared with the once-every-3-weeks regimen. Therefore, no significant accumulation of acMMAE was observed, even when the drug was administrated weekly.

One (1%) of the 75 tested patients who were evaluable for postdose anti-DSTP3086S antibodies was confirmed positive for antidrug antibodies. No differences were observed in the PK profiles, safety features, or efficacy outcomes for this patient (data not shown).

Clinical Activity

For patients on the once-every-3-weeks dosing schedule, a waterfall plot of the best PSA percent change from baseline is shown in Figure 2. In aggregate, 11 (14%; 95% CI, 7% to 24%) of 77 patients met the response criteria of a confirmed PSA reduction of ≥ 50%. After restricting to patients treated with DSTP3086S at doses > 2 mg/kg (n = 62), PSA responses were obtained in one (14%; 95% CI, 0% to 58%) of seven at the 2.25 mg/kg, five (13%; 95% CI, 4% to 27%) of 39 at the 2.4 mg/kg, and five (31%; 95% CI, 11% to 59%) of 16 at the 2.8 mg/kg dose levels. PSA changes relative to baseline for patients with PSA responses are shown in the Data Supplement.

Of the 46 patients with evaluable disease per RECIST at baseline, two (4%) had a partial response (one confirmed)

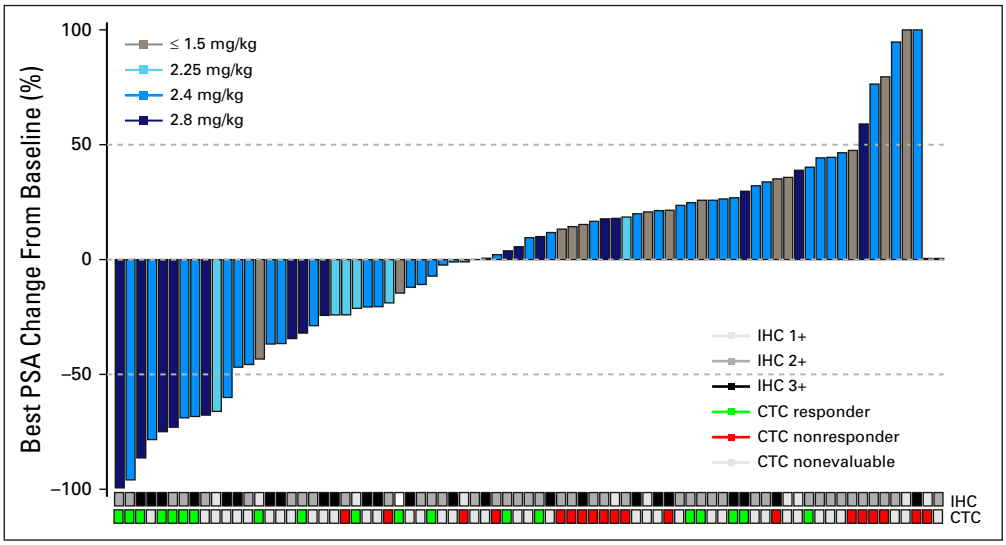


FIG 2. Best response by DSTP3086S once-every-3-weeks dose cohort. Waterfall plot showing best prostate-specific antigen (PSA) change from baseline and corresponding six-transmembrane epithelial antigen of the prostate 1 immunohistochemistry (IHC) and circulating tumor cell (CTC) conversion status. Dashed lines indicate ± 50% change from baseline.

and 24 (52%) stable disease as best radiographic response. Both patients with partial responses belonged to the subset of 36 evaluable patients per RECIST who received DSTP3086S at doses > 2 mg/kg.

Fourteen patients (18%) remained on study treatment for ≥ 6 months (Fig 1), including two patients with a partial response (Fig 3). One was a 72-year-old man with prostatectomy tumor biopsy tissue that demonstrated IHC 2+ STEAP1 expression. This patient had progressive CRPC after successive treatments with bicalutamide, docetaxel, abiraterone, cabozantinib, and palliative radiation therapy. He received DSTP3086S at a starting dose of 2.8 mg/kg and demonstrated a partial response after cycle 4 (confirmed on subsequent imaging), with a maximum PSA decline of 99%. At cycle 10, DSTP3086S dose was reduced to 2.25 mg/kg because of grade 2 peripheral sensory neuropathy, and the patient discontinued study treatment at cycle 13 as a result of disease progression.

The second patient was a 60-year-old man with prostatectomy tumor biopsy tissue that exhibited IHC 3+ STEAP1 expression. This patient had progressive CRPC after bicalutamide, apalutamide, abiraterone, and docetaxel and received DSTP3086S at a starting dose of 2.8 mg/kg, which was reduced to 2.25 mg/kg at cycle 3 because of grade 3 pulmonary embolism. He demonstrated an unconfirmed radiographic partial response after cycle 4 and a maximum PSA decline of 86% from baseline. He continued on study treatment until cycle 8 and discontinued DSTP3086S as a result of disease progression.

In the weekly cohorts, two patients remained on study treatment for ≥ 6 months. No patients achieved a PSA or RECIST response.

Biomarker Analysis

Among the 134 patients screened for the study, tumor STEAP1 protein expression by IHC was as follows: IHC 0 in one (1%), IHC 1+ in 35 (26%), IHC 2+ in 65 (49%), and IHC 3+ in 33 (24%). Given that only patients with IHC 2+ or 3+ tumor were eligible for the expansion cohorts, most had high STEAP1-expressing tumors (Fig 2). Of the 11 patients with PSA declines of ≥ 50% from baseline, one (10%) had IHC 1+, five (45%) had IHC 2+, and five (45%) had IHC 3+ tumors. At doses of > 2 mg/kg, one (20%) of five patients with IHC 1+ tumors, five (14%) of 36 with IHC 2+ tumors, and five (24%) of 21 with IHC 3+ tumors had PSA declines of ≥ 50% from baseline.

Of the 77 patients who received DSTP3086 once every 3 weeks, 38 (49%; 95% CI, 38% to 61%) had baseline CTCs ≥ 5/7.5 mL of blood. CTC conversions from ≥ 5 to < 5 cells/7.5 mL of blood after treatment were observed in 19 (50%; 95% CI, 33% to 67%) of 38 patients and in 16 (59%; 95% CI, 39% to 78%) of 27 patients who received DSTP3086S at doses > 2 mg/kg. By dose level, of the CTC-informative patients, CTC conversions were observed in three (27%; 95% CI, 6% to 61%) of 11 patients treated at doses < 1.5 mg/kg, one (20%; 95% CI, 1% to 72%) of five patients at 2.25 mg/kg, seven (64%; 95% CI, 31% to 89%) of 11 patients at 2.4 mg/kg, and eight (73%; 95% CI, 39% to 94%) of 11 patients at 2.8 mg/kg. Of the 19 CTC converters, the median baseline (pretreatment) CTC count was 31 cells (range, 6 to 304 cells), with 14 (74%) of 19 patients having baseline CTCs > 10/7.5 mL of blood. No patients on the weekly dose schedule demonstrated a CTC conversion.

Among the patients treated once every 3 weeks with DSTP3086S, 53 (69%; 95% CI, 57% to 79%) of 77 had baseline CTCs ≥ 1/7.5 mL of blood, 18 of whom converted to 0 (34%; 95% CI, 22% to 48%) detectable CTCs on DSTP3086S treatment. This represented 18 (45%; 95% CI, 29% to 62%) of 40 patients treated with DSTP3086S > 2 mg/kg once every 3 weeks *v* zero (0%; 95% CI, 0% to 25%) of 13 patients who received DSTP3086S ≤ 1.5 mg/kg once every 3 weeks.[18]

DISCUSSION

ADCs are designed to deliver potent cytotoxic agents directly to tumors that overexpress the target antigen while improving the therapeutic index by reducing normal tissue exposure.[23] DSTP3086S is a novel ADC that targets the STEAP1 antigen frequently expressed in prostate cancer (73% IHC 2+/3+ in patients screened for this trial). In this study, the RP2D of 2.4 mg/kg once every 3 weeks showed preliminary evidence of antitumor activity in patients with progressive mCRPC, including those with prior exposure to microtubule inhibitors. Patients enrolled in the study were enriched for high STEAP1-expressing tumors because they were considered to be the most likely to benefit from DSTP3086S treatment. Antitumor activity was assessed by PSA changes, imaging, and novel CTC-based measurements to broadly investigate potential clinical benefit. Although DSTP3086S would require refinement to optimize its therapeutic index for further clinical development, the phase I data support the feasibility of targeting STEAP1 in mCRPC. As such, the data may be a valuable guide for novel therapeutic modalities, such as improved ADCs, chimeric antigen receptor T cells, and immune cell–recruiting bispecific antibodies that target STEAP1.

Overall, there was a general concordance between measures of antitumor activity (ie, PSA changes, CTC conversions, RECIST changes; Figs 1 to 3). Clinical activity was evident at dose levels > 2 mg/kg as shown by ≥ 50% declines in PSA in 18% of patients, although only two

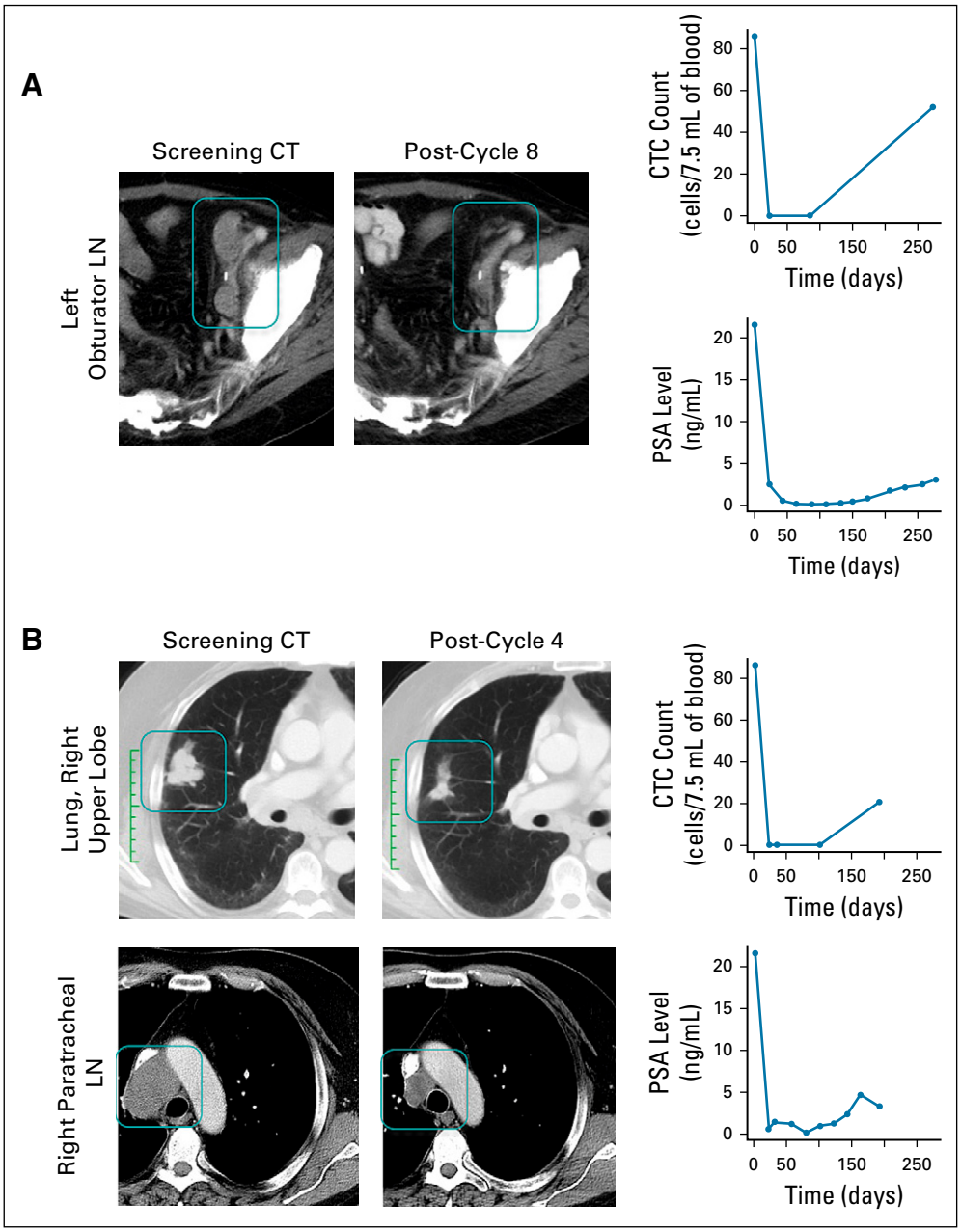


FIG 3. Patient vignettes. (A) A 72-year-old man with six-transmembrane epithelial antigen of the prostate 1 immunohistochemistry 2+ prostate cancer. This patient received DSTP3086S at 2.8 mg/kg and demonstrated a partial response after cycle 4 that was confirmed on subsequent imaging and a maximum prostate-specific antigen (PSA) decline of 99%. The patient discontinued study treatment at cycle 13 as a result of disease progression on the basis of a rising PSA level. (B) A 60-year-old man with six-transmembrane epithelial antigen of the prostate 1 immunohistochemistry 3+ prostate cancer. This patient received DSTP3086S at 2.8 mg/kg, which was reduced to 2.25 mg/kg at cycle 3 because of grade 3 pulmonary embolism. He demonstrated a maximum PSA decline of 86% and an unconfirmed radiographic partial response after cycle 4. Study treatment continued until cycle 8 and was discontinued as a result of disease progression. CT, computed tomography; CTC, circulating tumor cell; LN, lymph node.

patients who received the highest tested dose of DSTP3086S 2.8 mg/kg once every 3 weeks achieved a partial radiographic response. This clinical activity was also noted in heavily pretreated patients.

Half of the patients who received DSTP3086S once every 3 weeks had informative baseline CTCs ≥ 5/7.5 mL of blood, where CTC conversion to favorable < 5 cells/7.5 mL of blood after treatment was observed in 50% of patients across all dose levels, with an increasing conversion rate of 64% in the 2.4 mg/kg cohort and 73% in the 2.8 mg/kg cohort. A biomarker panel containing CTC conversions has been shown to be a surrogate for survival at the individual-patient level in trials with novel anti-androgens, such as abiraterone acetate (28% of CTC-informative patients converted) and enzalutamide (24% of CTC-informative patients converted).[18,21] Although PSA declines and imaging responses with STEAP1-ADC treatment were not common, half of the patients with evaluable CTCs had CTC conversions, some coupled with prolonged disease stability. This suggests activity for STEAP1-ADC that is reflected by CTC conversion rather than by PSA or imaging responses and warrants further investigation. In general, the number of prior treatments (either docetaxel or androgen receptor directed) correlated with worse response to DSTP3086S. A limited number of chemotherapy-naïve patients enrolled in the initial 2.4 mg/kg expansion cohort. Because of an overlapping mechanism of action and toxicity between systemic taxanes and MMAE delivered by DSTP3086S, an additional 17 patients were enrolled to assess DSTP3086S in those who had received abiraterone and/or enzalutamide but were chemotherapy naïve; notably only one PSA response was observed. This suggests that prior chemotherapy exposure is not the only factor that potentially limits DSTP3086S activity.

The PK of DSTP3086S was linear across all doses assessed, driven mainly by the anti-STEAP1 antibody, and is consistent with the behavior observed with other ADCs. Dosing on a weekly schedule did not improve overall drug safety, tolerability, or efficacy compared with once every 3 weeks. Fatigue, peripheral neuropathy, and GI symptoms were the most frequent related AEs observed. Dosing at 2.8 mg/kg required more dose reductions compared with 2.4 mg/kg dosing. Therefore, 2.4 mg/kg was selected as the RP2D.

The relationship between exposure and safety events (eg, neuropathy) is unclear given the small number of patients treated at different doses. The development of peripheral neuropathy with repeated dosing, a known AE associated with microtubule inhibition, is likely mediated by the MMAE therapeutic payload.[24-27] Hyperglycemia was reported as an AE in 13% of patients in the study. The mechanism for a potential association between DSTP3086S and hyperglycemia remains unclear, although possibly related to MMAE given reports of hyperglycemia with other ADCs conjugated to MMAE.[28-30]

Evaluation of STEAP1 IHC scores suggests a potential association between STEAP1 expression and DSTP3086S clinical activity. However, even with high tumor STEAP1 expression (IHC 3+), the majority of patients did not achieve PSA responses, and the underlying reasons behind intrinsic resistance to DSTP3086S are unknown. It is unknown whether acquired loss of STEAP1 expression after DSTP3086S treatment could explain resistance after an initial response. One effort to better understand STEAP1 expression in patients with CRPC subsequently treated with DSTP3086 was anti-STEAP1-desferrioxamine-^{89}Zr–based positron emission tomography imaging.[31]

In summary, DSTP3086S demonstrated an acceptable safety profile, with evidence of antitumor activity confirming that the targeting of STEAP1-expressing mCRPC tumors with an ADC is feasible. Although DSTP3086S would require optimization for further clinical development, these data may inform development of novel ADCs, chimeric antigen receptor T cells, and immune cell–recruiting bispecific antibodies that target STEAP1.

AFFILIATIONS

[1]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY
[2]The University of Chicago, Chicago, IL
[3]Karmanos Cancer Institute, Detroit, MI
[4]University of Washington and Fred Hutchinson Cancer Research Center, Seattle, WA
[5]California Pacific Medical Center, San Francisco, CA
[6]Genentech, South San Francisco, CA

CORRESPONDING AUTHOR

Daniel C. Danila, MD, Genitourinary Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10065; Twitter: @sloan_kettering, @ThePCCTC; e-mail: danilad@mskcc.org.

PRIOR PRESENTATION

Presented at the 2013 Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, May 31-June 4, 2013; 2014 Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, May 30-June 3, 2014; 2015 Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, May 29-June 2, 2015; and American Association for Cancer Research 106th Annual Meeting, Philadelphia, PA, April 18-22, 2015.

SUPPORT

Supported by Genentech. Genentech was involved in the study design, data interpretation, and the decision to submit for publication in conjunction with the authors. National Cancer Institute Cancer Center Support Grant No. P30 CA008748 (D.C.D, H.I.S), Department of Defense Prostate Cancer Research Program Physician Research Award W81XWH-09–1-0307 (D.C.D) and the Prostate Cancer Clinical Trials Consortium.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.19.00646.

AUTHOR CONTRIBUTIONS

Conception and design: Daniel C. Danila, Celestia S. Higano, Houston N. Gilbert, Omar Kabbarah, Michael Mamounas, Bernard M. Fine, Daniel J. Maslyar, Howard I. Scher

Administrative support: Howard I. Scher

Provision of study material or patients: Daniel C. Danila, Russell Z. Szmulewitz, Ulka Vaishampayan, Ari D. Baron, Howard I. Scher

Collection and assembly of data: Daniel C. Danila, Russell Z. Szmulewitz, Ulka Vaishampayan, Celestia S. Higano, Ari D. Baron, Houston N. Gilbert, Marija Milojic-Blair, Omar Kabbarah, Daniel J. Maslyar, Howard I. Scher

Data analysis and interpretation: Daniel C. Danila, Ulka Vaishampayan, Celestia S. Higano, Houston N. Gilbert, Flavia Brunstein, Marija Milojic-Blair, Bei Wang, Omar Kabbarah, Michael Mamounas, Bernard M. Fine, Daniel J. Maslyar, Alexander Ungewickell, Howard I. Scher

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

We thank the patients, study investigators, and staff who participated in this study. Writing assistance was provided by Genentech.

REFERENCES

1. Ryan CJ, Smith MR, de Bono JS, et al: Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 368:138-148, 2013
2. de Bono JS, Logothetis CJ, Molina A, et al: Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 364:1995-2005, 2011
3. Scher HI, Fizazi K, Saad F, et al: Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 367:1187-1197, 2012
4. Parker C, Nilsson S, Heinrich D, et al: Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med 369:213-223, 2013
5. de Bono JS, Oudard S, Ozguroglu M, et al: Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: A randomised open-label trial. Lancet 376:1147-1154, 2010
6. Beer TM, Armstrong AJ, Rathkopf DE, et al: Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 371:424-433, 2014
7. Ryan CJ, Smith MR, Fizazi K, et al: Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): Final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 16:152-160, 2015
8. Gomes IM, Maia CJ, Santos CR: STEAP proteins: From structure to applications in cancer therapy. Mol Cancer Res 10:573-587, 2012
9. Hubert RS, Vivanco I, Chen E, et al: STEAP: A prostate-specific cell-surface antigen highly expressed in human prostate tumors. Proc Natl Acad Sci U S A 96:14523-14528, 1999
10. Challita-Eid PM, Morrison K, Etessami S, et al: Monoclonal antibodies to six-transmembrane epithelial antigen of the prostate-1 inhibit intercellular communication in vitro and growth of human tumor xenografts in vivo. Cancer Res 67:5798-5805, 2007
11. Danila DC, Scher HI, Szafer-Glusman E, et al: Predictive biomarkers of tumor sensitivity to STEAP1 antibody-drug conjugate in patients with metastatic castration-resistant prostate cancer. Cancer Res 75, 2015 (suppl; abstr 4310)
12. Bai RL, Pettit GR, Hamel E: Binding of dolastatin 10 to tubulin at a distinct site for peptide antimitotic agents near the exchangeable nucleotide and vinca alkaloid sites. J Biol Chem 265:17141-17149, 1990
13. Doronina SO, Toki BE, Torgov MY, et al: Development of potent monoclonal antibody auristatin conjugates for cancer therapy. Nat Biotechnol 21:778-784, 2003 [Erratum: Nat Biotechnol 21:941, 2003]
14. Francisco JA, Cerveny CG, Meyer DL, et al: cAC10-vcMMAE, an anti-CD30-monomethyl auristatin E conjugate with potent and selective antitumor activity. Blood 102:1458-1465, 2003
15. Scher HI, Halabi S, Tannock I, et al: Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: Recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 26:1148-1159, 2008
16. Therasse P, Arbuck SG, Eisenhauer EA, et al: New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205-216, 2000
17. de Bono JS, Scher HI, Montgomery RB, et al: Circulating tumor cells predict survival benefit from treatment in metastatic castration-resistant prostate cancer. Clin Cancer Res 14:6302-6309, 2008
18. Heller G, McCormack R, Kheoh T, et al: Circulating tumor cell number as a response measure of prolonged survival for metastatic castration-resistant prostate cancer: A comparison with prostate-specific antigen across five randomized phase III clinical trials. J Clin Oncol 36:572-580, 2018
19. Heller G, Fizazi K, McCormack R, et al: The added value of circulating tumor cell enumeration to standard markers in assessing prognosis in a metastatic castration-resistant prostate cancer population. Clin Cancer Res 23:1967-1973, 2017
20. Scher HI, Jia X, de Bono JS, et al: Circulating tumour cells as prognostic markers in progressive, castration-resistant prostate cancer: A reanalysis of IMMC38 trial data. Lancet Oncol 10:233-239, 2009
21. Scher HI, Heller G, Molina A, et al: Circulating tumor cell biomarker panel as an individual-level surrogate for survival in metastatic castration-resistant prostate cancer. J Clin Oncol 33:1348-1355, 2015
22. Scher HI, Graf RP, Schreiber NA, et al: Phenotypic heterogeneity of circulating tumor cells informs clinical decisions between AR signaling inhibitors and taxanes in metastatic prostate cancer. Cancer Res 77:5687-5698, 2017
23. Verma S, Miles D, Gianni L, et al: Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med 367:1783-1791, 2012
24. Argyriou AA, Bruna J, Marmiroli P, et al: Chemotherapy-induced peripheral neurotoxicity (CIPN): An update. Crit Rev Oncol Hematol 82:51-77, 2012
25. Advani RH, Lebovic D, Chen A, et al: Phase I study of the anti-CD22 antibody-drug conjugate pinatuzumab vedotin with/without rituximab in patients with relapsed/refractory B-cell non-Hodgkin lymphoma. Clin Cancer Res 23:1167-1176, 2017
26. Liu JF, Moore KN, Birrer MJ, et al: Phase I study of safety and pharmacokinetics of the anti-MUC16 antibody-drug conjugate DMUC5754A in patients with platinum-resistant ovarian cancer or unresectable pancreatic cancer. Ann Oncol 27:2124-2130, 2016
27. Stagg NJ, Shen BQ, Brunstein F, et al: Peripheral neuropathy with microtubule inhibitor containing antibody drug conjugates: Challenges and perspectives in translatability from nonclinical toxicology studies to the clinic. Regul Toxicol Pharmacol 82:1-13, 2016

28. Gopal AK, Ramchandren R, O'Connor OA, et al: Safety and efficacy of brentuximab vedotin for Hodgkin lymphoma recurring after allogeneic stem cell transplantation. Blood 120:560-568, 2012
29. Weekes CD, Lamberts LE, Borad MJ, et al: Phase I study of DMOT4039A, an antibody-drug conjugate targeting mesothelin, in patients with unresectable pancreatic or platinum-resistant ovarian cancer. Mol Cancer Ther 15:439-447, 2016
30. McHugh D, Eisenberger M, Heath EI, et al: A phase I study of the antibody drug conjugate ASG-5ME, an SLC44A4-targeting antibody carrying auristatin E, in metastatic castration-resistant prostate cancer. Invest New Drugs 37:1052-1060, 2019
31. Carrasquillo JA, Danila DC, Beylergil V, et al: Initial PET imaging and pharmacokinetic results from a phase I/II study of Zr-89-labeled anti-STEAP1 antibody in metastatic castrate-resistant prostate cancer (mCRPC) patients. Cancer Res 74, 2014 (suppl; abstr 2069)

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Phase I Study of DSTP3086S, an Antibody-Drug Conjugate Targeting Six-Transmembrane Epithelial Antigen of Prostate 1, in Metastatic Castration-Resistant Prostate Cancer

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Daniel C. Danila
Honoraria: Angle, Bayer AG, ScreenCell
Consulting or Advisory Role: Angle, Bayer AG, Sanador
Research Funding: Prostate Cancer Foundation, Genentech, Janssen Pharmaceuticals (Inst)
Patents, Royalties, Other Intellectual Property: Gene Expression Profile Associated With Prostate Cancer
Travel, Accommodations, Expenses: Cambridge Healthtech Institute, Prostate Cancer Foundation, Angle, Bayer AG, American Austrian Open Medical Institute, Global Technology Community, Oncology Education, ScreenCell, StopCancer

Russell Z. Szmulewitz
Honoraria: Astellas Pharma
Consulting or Advisory Role: AstraZeneca, AbbVie, Exelixis, Merck, Amgen, Janssen Pharmaceuticals, Sanofi, Astellas Pharma, Pfizer
Research Funding: AbbVie, Astellas Pharma, Incyte, Macrogenics, Janssen Pharmaceuticals
Patents, Royalties, Other Intellectual Property: Co-inventor on patent licensed by The University of Chicago to Corcept Therapeutics for combination androgen receptor/glucocorticoid receptor inhibition in prostate cancer
Travel, Accommodations, Expenses: Corcept Therapeutics

Ulka Vaishampayan
Honoraria: Pfizer, Bayer AG, Sanofi, Bristol-Myers Squibb, Exelixis
Consulting or Advisory Role: Pfizer, Bristol-Myers Squibb, Exelixis, Bayer AG, EMD Serono
Speakers' Bureau: Pfizer, Bayer AG, Bristol-Myers Squibb, Exelixis, Sanofi, Eisai
Research Funding: Astellas Pharma, Exelixis, Pfizer, Bristol-Myers Squibb

Celestia S. Higano
Employment: CTI (I)
Leadership: CTI (I)
Stock and Other Ownership Interests: CTI (I)
Consulting or Advisory Role: Bayer AG, Ferring Pharmaceuticals, Astellas Pharma, Blue Earth Diagnostics, Myriad Genetics, Tolmar, Janssen Pharmaceuticals, Hinova Pharmaceuticals, Pfizer, AstraZeneca
Research Funding: Aragon Pharmaceuticals (Inst), AstraZeneca (Inst), Dendreon (Inst), Medivation (Inst), Emergen BioSolutions (Inst), Bayer AG (Inst), Pfizer (Inst), Roche (Inst), Astellas Pharma (Inst)
Travel, Accommodations, Expenses: Bayer AG, Astellas Pharma, Clovis Oncology, Blue Earth Diagnostics, Ferring Pharmaceuticals, Menarini, Myriad Genetics, Pfizer, Hinova Pharmaceuticals

Ari D. Baron
Speakers' Bureau: Bristol-Myers Squibb, Genentech, Roche, Merck, Eli Lilly, Amgen, Eisai, Johnson & Johnson, AbbVie

Houston N. Gilbert
Employment: Genentech, Roche, Bellicum Pharmaceuticals, Arcus Biosciences
Stock and Other Ownership Interests: Denali Therapeutics, Celgene, Bellicum Pharmaceuticals
Patents, Royalties, Other Intellectual Property: "Methods of Using Anti-STEAP1 Antibodies for the Treatment of Cancer" (or similar). US and European Union patent applications were submitted following exploratory analysis conducted during a trial of DSTP3086S, a vc-MMAE-anti-STEAP1 ADC (Inst)

Flavia Brunstein
Employment: Roche, Genentech
Stock and Other Ownership Interests: Roche, Genentech

Marija Milojic-Blair
Employment: Genentech, Roche

Bei Wang
Employment: Genentech, Roche
Stock and Other Ownership Interests: Genentech, Roche

Omar Kabbarah
Employment: Genentech
Stock and Other Ownership Interests: Genentech

Michael Mamounas
Employment: Genentech, Amgen (I)
Stock and Other Ownership Interests: Genentech, Amgen (I)
Travel, Accommodations, Expenses: Genentech, Amgen (I)

Bernard M. Fine
Employment: Genentech
Stock and Other Ownership Interests: Roche
Travel, Accommodations, Expenses: Genentech

Daniel J. Maslyar
Employment: Genentech, Alector
Stock and Other Ownership Interests: Genentech, Alector
Consulting or Advisory Role: Western Oncolytics

Alexander Ungewickell
Employment: Genentech
Stock and Other Ownership Interests: Seattle Genetics, Bristol-Myers Squibb, Agios, Alnylam, Regeneron Pharmaceuticals, Rosetta Genomics, Genentech, Roche, Alexion Pharmaceuticals, Amicus Therapeutics

Howard I. Scher
Leadership: Asterias Biotherapeutics
Stock and Other Ownership Interests: Asterias Biotherapeutics
Consulting or Advisory Role: Janssen Pharmaceuticals, Amgen, Menarini Silicon Biosystems, WIRB-Copernicus Group, ESSA, OncLive Insights, Physician Education Resource, Sanofi, Ambry Genetics, Konica Minolta, Bayer AG
Research Funding: Janssen Pharmaceuticals (Inst), Innocrin Pharma (Inst), Illumina (Inst), Epic Sciences (Inst), Menarini Silicon Biosystems (Inst), Thermo Fisher Scientific (Inst)
Travel, Accommodations, Expenses: Asterias Biotherapeutics, Physician Education Resource, Menarini Silicon Biosystems, Amgen, WIRB-Copernicus Group, Konica Minolta, OncLive Insights, ESSA, Prostrate Cancer Foundation, Sanofi, Bayer AG

No other potential conflicts of interest were reported.

Published OnlineFirst July 21, 2020; DOI: 10.1158/1078-0432.CCR-20-1707

A Phase Ib/IIa Study of the Pan-BET Inhibitor ZEN-3694 in Combination with Enzalutamide in Patients with Metastatic Castration-resistant Prostate Cancer

Rahul R. Aggarwal[1], Michael T. Schweizer[2], David M. Nanus[3], Allan J. Pantuck[4], Elisabeth I. Heath[5], Eric Campeau[6], Sarah Attwell[6], Karen Norek[6], Margo Snyder[6], Lisa Bauman[6], Sanjay Lakhotia[6], Felix Y. Feng[1], Eric J. Small[1], Wassim Abida[7], and Joshi J. Alumkal[8,9]

ABSTRACT

Purpose: ZEN-3694 is a bromodomain extraterminal inhibitor (BETi) with activity in androgen-signaling inhibitor (ASI)-resistant models. The safety and efficacy of ZEN-3694 plus enzalutamide was evaluated in a phase Ib/IIa study in metastatic castration-resistant prostate cancer (mCRPC).

Patients and Methods: Patients had progressive mCRPC with prior resistance to abiraterone and/or enzalutamide. 3+3 dose escalation was followed by dose expansion in parallel cohorts (ZEN-3694 at 48 and 96 mg orally once daily, respectively).

Results: Seventy-five patients were enrolled ($N = 26$ and 14 in dose expansion at low- and high-dose ZEN-3694, respectively). Thirty (40.0%) patients were resistant to abiraterone, 34 (45.3%) to enzalutamide, and 11 (14.7%) to both. ZEN-3694 dosing ranged from 36 to 144 mg daily without reaching an MTD. Fourteen patients (18.7%) experienced grade ≥3 toxicities, including three patients with grade 3 thrombocytopenia (4%). An exposure-dependent decrease in whole-blood RNA expression of BETi targets was observed (up to fourfold mean difference at 4 hours post–ZEN-3694 dose; $P \leq 0.0001$). The median radiographic progression-free survival (rPFS) was 9.0 months [95% confidence interval (CI), 4.6–12.9] and composite median radiographic or clinical progression-free survival (PFS) was 5.5 months (95% CI, 4.0–7.8). Median duration of treatment was 3.5 months (range, 0–34.7+). Lower androgen receptor (AR) transcriptional activity in baseline tumor biopsies was associated with longer rPFS (median rPFS 10.4 vs. 4.3 months).

Conclusions: ZEN-3694 plus enzalutamide demonstrated acceptable tolerability and potential efficacy in patients with ASI-resistant mCRPC. Further prospective study is warranted including in mCRPC harboring low AR transcriptional activity.

Introduction

Prostate cancer is the most common malignancy and second leading cause of death among men in the United States (1). Androgen-signaling blockade with either androgen receptor (AR) antagonism or CYP17 inhibition improves long-term survival in both metastatic castration-resistant prostate cancer (mCRPC) and metastatic castration-sensitive disease (2–5). However, treatment resistance is universal, and cross-resistance between AR antagonists and CYP17 inhibitors limits the clinical utility of these agents when used sequentially (6–10).

Multiple mechanisms of therapeutic resistance to AR pathway inhibitors have been described, including amplification of the *AR* gene and its enhancers, upregulation of intratumoral androgen synthesis, generation of ligand-independent AR splice variants, activation of alternative oncogenic signaling pathways including MYC, transdifferentiation to an AR-independent, neuroendocrine phenotype, and cooption of alternative steroid hormone receptors including the glucocorticoid receptor (GR; refs. 11–16). A broad therapeutic approach capable of affecting expression/signaling of multiple pathways may provide a means to reverse resistance and restore sensitivity to AR-targeting therapy.

Proteins of the bromodomain extraterminal (BET) bromodomain family are epigenetic readers that bind to acetylated histones through their bromodomains to affect gene transcription (17). They preferentially localize at sites of enhancers of various oncogenes to promote tumorigenesis and progression. ZEN-3694 is an orally bioavailable, second-generation, potent pan-BET bromodomain inhibitor (BETi) that leads to downregulation of expression of AR signaling, AR splice variants, MYC, GR, and other oncogenes in multiple CRPC models, and has significant *in vivo* activity as single agents, with evidence of synergy when combined with enzalutamide (18).

We conducted a first-in-human phase Ib/II dose-escalation/expansion study of ZEN-3694 in combination with enzalutamide in patients with mCRPC and prior progression on one or more androgen-signaling inhibitor (ASI).

Patients and Methods

Patient population

Patients had histologically confirmed mCRPC with progression at study entry by Prostate Cancer Working Group 2 (PCWG2)

[1]University of California, San Francisco, San Francisco, California. [2]University of Washington and Fred Hutchinson Cancer Research Center, Seattle, Washington. [3]Weill-Cornell Medicine, New York, New York. [4]University of California, Los Angeles, Los Angeles, California. [5]Karmanos Cancer Institute, Wayne State University, Detroit, Michigan. [6]Zenith Epigenetics Ltd., Calgary, Alberta, Canada. [7]Memorial Sloan Kettering Cancer Center, New York, New York. [8]Oregon Health & Science University, Portland, Oregon. [9]University of Michigan Rogel Cancer Center, Ann Arbor, Michigan.

Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

W. Abida and J. Alumkal contributed equally to this article.

Corresponding Authors: Rahul Aggarwal, University of California, San Francisco, 1600 Divisadero Street, Room A717, Box 1711, San Francisco, CA 94143-1711. Phone: 415-353-9278; Fax: 415-353-7779; E-mail: rahul.aggarwal@ucsf.edu; Joshi Alumkal, 1500 E Medical Center Drive, Ann Arbor, MI 48109. E-mail: jalumkal@med.umich.edu; and Wassim Abida, 1275 York Avenue, New York, NY 10065. E-mail: abidam@mskcc.org

Clin Cancer Res 2020;XX:XX–XX

doi: 10.1158/1078-0432.CCR-20-1707

Published OnlineFirst July 21, 2020; DOI: 10.1158/1078-0432.CCR-20-1707

Translational Relevance

Bromodomain extraterminal inhibitors (BETi) demonstrate *in vivo* activity in enzalutamide-resistant prostate cancer models via downregulation of bypass signaling pathways including MYC. Clinical translation of BETi as a therapeutic strategy in metastatic castration-resistant prostate cancer (mCRPC) has heretofore been limited by significant toxicity including risk of thrombocytopenia. In this phase Ia/IIb study of the pan-BETi, ZEN-3694, in combination with enzalutamide in 75 patients with abiraterone- and/or enzalutamide-resistant mCRPC, the combination was well-tolerated without reaching an MTD. Less than 5% of patients experienced a grade ≥3 thrombocytopenia. Robust, dose-dependent, and sustained downregulation of expression of BETi target genes including *MYC* was observed using a whole-blood RNA assay. Encouraging efficacy was observed including a median radiographic progression-free survival of more than 10 months in those with prior progression on enzalutamide monotherapy. Clinical benefit was particularly pronounced in high-risk subgroups including those with an aggressive variant clinical phenotype as well as those with lower androgen receptor transcriptional activity in baseline tumor biopsies. A randomized study is planned with ZEN-3694 at the recommended phase II dose of 96 mg orally once daily in combination with enzalutamide in mCRPC with prior progression on enzalutamide or abiraterone.

criteria (19). Patients were required to have progression on prior abiraterone and/or enzalutamide treatment prior to study entry, no prior docetaxel for the treatment of mCRPC, serum testosterone <50 ng/dL with maintenance of androgen deprivation therapy during study treatment, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, adequate organ function including absolute neutrophil count >1.5 × 10^9/L, platelet count >100,000, total bilirubin <1.5 × ULN, and creatinine clearance >60 mL/minute. Patients with uncontrolled hypertension or New York Heart Association class II or higher congestive heart failure were excluded.

Study approval was obtained from the ethics committees at the participating institutions and regulatory authorities. All patients gave written informed consent. The study followed the Declaration of Helsinki and Good Clinical Practice guidelines (NCT02711956).

Study design and treatment schedule

This was a phase Ib/II, multicenter, open-label, combination dose-escalation study of ZEN-3694 in combination with the standard dose of enzalutamide, 160 mg daily. Lead-in treatment period with enzalutamide monotherapy (day −14 to day −1) was required in subjects not already receiving enzalutamide at the time of study enrollment. Patients continued treatment until radiographic progression by PCWG2 criteria, unequivocal clinical progression, or unacceptable toxicity. PSA progression alone was not used as a criterion for treatment discontinuation.

The starting dose of ZEN-3694 was 36 mg orally once daily. A 3+3 dose-escalation schema was utilized up to a maximum administered dose of 144 mg daily. Dose expansion was subsequently performed in two cohorts in parallel: (i) low dose, ZEN-3694 at 48 mg daily ($N = 14$), and (ii) high dose, ZEN-3694 96 mg daily ($N = 26$).

A formal interim analysis was not planned; however, interim data were reviewed on an ongoing basis. The final planned analyses were performed after 75 patients were enrolled and the database was locked on February 6, 2020.

The primary study endpoint was safety and the recommended phase II dose of ZEN-3694 in combination with enzalutamide. Secondary endpoints included pharmacokinetics assessment of ZEN-3694 and enzalutamide, PSA50 response (≥50% decline in PSA from baseline confirmed ≥4 weeks later) rate, duration of PSA50 response, and radiographic progression-free survival (rPFS). Soft-tissue radiographic progression and responses were assessed according to RECIST v1.1 criteria. Progression of bone metastases was assessed using PCWG2 criteria. *Post hoc* analyses were performed to assess composite progression-free survival (PFS), defined as first occurrence of radiographic or clinical progression or death, as well as PSA PFS by PCWG2 criteria. Correlative endpoints included pharmacodynamics assessment of ZEN-3694 in combination with enzalutamide and relationship between tumor genomic/transcriptional profile, protein expression, and clinical variables with clinical outcomes on treatment.

Safety and efficacy assessments

Clinical and laboratory assessments were conducted at baseline and weekly during cycles 1 and 2 (28-day cycle length), every 2 weeks in cycle 3, and then every 4 weeks thereafter. Tumor response monitoring was performed using whole-body bone scan and cross-sectional imaging of the chest/abdomen/pelvis at baseline and every 2 cycles thereafter. Adverse events were graded using Common Toxicity Criteria version 4.0.

Pharmacodynamic/exploratory assessments

Whole-blood RNA for assessment of BETi target gene expression (*MYC, IL8, CCR1*, GPR183, HEXIM1, and *IL1RN*) was collected predose, 2 hours, 4 hours, 6 hours, and 24 hours post–cycle 1, day 1 dose (20). Baseline and on-treatment metastatic tumor biopsies of bone or soft tissue were obtained whenever feasible, and were evaluated by RNA-sequencing (RNA-seq) and IHC for protein expression of AR. Quality of the FASTQ files was verified by FASTQC2, and reads were aligned on BaseSpace (https://basespace.illumina.com) using the RNA-Seq alignment App (version 1.1.1) with the default parameters (STAR aligner version 2.5.0b, UCSC hg19 reference genome). Gene expression levels (FPKM) for baseline biopsies were estimated using Cufflinks (version 2.2.1). For the paired biopsies, aligned reads were used as input for DESeq2 (version 1.1.0) to enable pairwise differential gene expression analysis using the default parameters. Gene set enrichment analysis (GSEA) was performed on transcriptional data when available, and previously validated AR, prostate cancer, and MYC transcriptional signatures were additionally applied to the transcriptional data (21, 22). For the BETi signature, significant genes ($P < 0.05$) that were >2-fold downregulated upon exposure of 0.5 μmol/L I-BET762 for 24 hours in LNCaP prostate cancer cells were selected (23). Archival tumor tissue was obtained whenever feasible for analysis of whole transcriptome and exome sequencing.

Pharmacokinetics assessments

Plasma levels of ZEN-3694, the bioactive first-order metabolite ZEN-3791, and enzalutamide were measured predose and up to 24 hours postdose on days 1 and 15 of cycle. Plasma concentrations were determined using validated LC/MS-MS analysis.

Published OnlineFirst July 21, 2020; DOI: 10.1158/1078-0432.CCR-20-1707

Table 1. Baseline characteristics.

	Study cohort ($N = 75$)[a]
Median age (range), years	70 (47–89)
ECOG score	
0	42 (56%)
1	33 (44%)
Opioid analgesic use	18 (24%)
Visceral metastases at study entry (%)	21 (28%)
Median PSA, ng/mL (range)	26.99 (0.15–1,701.8)
Median ALP, U/L (range)	82 (33–487)
Median LDH, U/L (range)	188 (98–543)
Median hemoglobin, g/dL (range)	13.2 (6.4–20.2)
Halabi risk category (ref. 24; %)	
Low	50 (67)
Intermediate	16 (21)
High	8 (11)
Unknown	1 (1)
Prior number of systemic cancer treatments (range)	3 (1–7)
Prior resistance to AR-targeted therapy (%)	
Abiraterone	30 (40)
Enzalutamide	34 (45)
Both	11 (15)
Duration of prior AR-targeted therapy (range), months	14.3 (1.0–58.3)
Reason for prior abiraterone or enzalutamide discontinuation	
Radiographic progression	8 (11%)
Radiographic and PSA progression	31 (41%)
Clinical and PSA progression	3 (4%)
PSA progression	33 (44%)
Clinical progression	0

Abbreviations: ALP, alkaline phosphatase; LDH, lactate dehydrogenase.
[a]For data recorded in the clinical database as of the data cut-off date of January 7, 2020.

Results

Study population and patient disposition

A total of 75 patients were enrolled from December 2016 to April 2019 across seven investigational sites. Baseline characteristics of the enrolled patients are shown in **Table 1**. At study entry, 30 (40.0%) patients had previously experienced disease progression on abiraterone, 34 (45.3%) on enzalutamide, and 11 (14.7%) on both. Twelve (16%) patients experienced prior primary resistance to first-line AR-targeted therapy, defined in *post hoc* fashion as treatment duration of less than 6 months. Forty-two (56%) patients had evidence of radiographic and/or clinical progression at study entry.

The median duration of treatment was 3.5 months (range, 0–34.7+). As of date of data cutoff, seven patients (9%) remain on treatment without progression, with duration of therapy ranging from 15.0+ to 34.7+ months. Forty-eight patients (64%) discontinued for disease progression; nine patients (12%) discontinued for adverse events, and 11 (16%) withdrew from study.

Safety results

The proportion of patients who experienced grade ≥3 treatment-related adverse event was 18.7% ($n = 14$). The most common grade ≥3 adverse events (≥2 patients) included nausea ($n = 3$; 4%), thrombocytopenia ($n = 3$; 4%), anemia ($n = 2$; 2.7%), fatigue ($n = 2$; 2.7%), and hypophosphatemia ($n = 2$; 2.7%). There were no clinically significant bleeding events observed on treatment.

The most commonly reported ZEN-3694–related adverse events (any grade severity, occurring in ≥10% of patients, in order of incidence) were visual symptoms (described as a transitory perception of brighter lights and/or light flashes, with or without visual color tinges, as well as trouble navigating in dim light; 67%), nausea (45%), fatigue (40%), decreased appetite (25%), dysgeusia (20%), thrombocytopenia (15%), and weight decreased (11%; **Table 2**). Visual symptoms were grade 1 in all cases, resolved 60–90 minutes after dosing, were successfully mitigated with implementation of dosing before bedtime, and resulted in no functional consequences upon repeat eye exams throughout study participation.

Dose reductions and/or treatment discontinuation due to adverse events were required in 24 of 75 (32%) of patients. The percentage of patients requiring dose reduction and/or discontinuation ranged from 10% to 35% for doses from 36 to 96 mg/day, in contrast to 75% and 100% at ZEN-3694 dose levels of 120 and 144 mg/day, respectively (Supplementary Table S1). The class of adverse events leading to dose reduction and/or discontinuation were related to gastrointestinal (GI) toxicities in 83% of occurrences.

Determination of MTD and recommended phase II dose

In the dose escalation, 35 patients were enrolled across dose levels ranging from 36 to 144 mg daily. The MTD was not reached. One patient experienced a dose-limiting toxicity at the 96 mg/day dose level (grade 3 nausea necessitating missing >25% of scheduled doses in cycle 1). On the basis of the aggregate of pharmacodynamics data indicating dose exposure–dependent downregulation of BETi target gene expression with a plateau of effect at doses above 96 mg/day, the high percentage of patients requiring dose interruptions/reductions at doses above 96 mg/day, and a comparable pharmacokinetics/pharmacodynamics effect with preclinical models treated at efficacious doses, 96 mg/day was chosen as the recommended phase II dose of ZEN-3694 for dose expansion ($N = 26$). An additional dose-expansion cohort of 48 mg/day ($N = 14$) was also enrolled, to better characterize the exposure–effect relationship.

Pharmacokinetics analyses

The AUC_{0-24} and the C_{max} of combined ZEN-3694 (parent compound) + ZEN-3791 (active metabolite), on day 1 and day 15 of cycle 1, are shown in **Fig. 1A** and **B**, respectively. Less than dose proportional increase in exposure was observed at doses higher than 96 mg daily. The estimated T_{max} and half-life of ZEN-3694 + ZEN-3791 were 2 and 5–6 hours, respectively. The ratio of ZEN-3791 metabolite to parent compound, ZEN-3694, was increased on day 15 compared with day 1, likely related to enzalutamide-mediated induction of CYP3A4 metabolism (**Fig. 1C**). The observed plasma concentrations of ZEN-3694 + ZEN-3791 were similar to ZEN-3694 monotherapy pharmacokinetics reported previously (24). Likewise, there was no significant impact of ZEN-3694 on enzalutamide and desmethyl enzalutamide concentrations (**Fig. 1D**).

Pharmacodynamics analyses

Pre- and up to 24-hour postdose whole-blood RNA analyses were available from 69 patients enrolled on study. There was a dose-dependent two- to fourfold decrease in the whole-blood mRNA levels of the BETi target genes *MYC, IL8, CCR1*, *GPR183*, and *IL1RN* (**Fig. 2A**) upon treatment with ZEN-3694, which was sustained for at least 8 hours. Decrease in expression of BETi target genes appeared to plateau at ZEN-3694 dose levels ≥96 mg. There was a direct correlation between cumulative exposure to ZEN-3694 + ZEN-3791 (AUC_{0-2} for *MYC* and *GPR183*, and AUC_{0-4} for *CCR1, IL1RN*, and

Published OnlineFirst July 21, 2020; DOI: 10.1158/1078-0432.CCR-20-1707

Table 2. Summary of all grades treatment-related adverse events by dose level of ZEN-3694.

	36 mg QD *n* = 4	48 mg QD *n* = 21	60 mg QD *n* = 6	72 mg QD *n* = 6	96 mg QD *n* = 31	120 mg QD *n* = 4	144 mg QD *n* = 3	Total *N* = 75 (%)
Blood creatinine increased			2		3			5 (6.7)
Constipation		1			3			4 (5.3)
Decreased appetite		2	2	1	10	3	2	20 (26.7)
Diarrhea				1	5			6 (8)
Dizziness				1	3			4 (5.3)
Dysgeusia		2	0	0	10	1	3	16 (21.3)
Dyspepsia		1			2			3 (4)
Fatigue	1	8	1	2	13	3	1	29 (38.7)
Nasal congestion					3			3 (4)
Nausea		7	2	3	17	3	2	34 (45.3)
Photopsia		1			3			4 (5.3)
Photosensitivity		2			3			5 (6.7)
Rash					3			3 (4)
Rash maculopapular		3			1		1	5 (6.7)
Taste disorder			1	1	3			5 (6.7)
Thrombocytopenia		1	1	2	6		1	11 (14.7)
Vision blurred					2	1		3 (4)
Visual symptoms[a]	3	12	4	6	17	4	2	48 (64)
Vomiting		1			3	1		5 (6.7)
Weight loss and abnormal weight loss	1			1	3	1	2	8 (10.7)

Abbreviation: QD, every day.
[a]Visual symptoms defined as a transitory perception of bright lights and/or light flashes with or without visual color tinges.

IL8) with downregulation of whole-blood mRNA levels of the BETi target genes (R^2 ranging from 0.20 to 0.51; $P \leq 0.0001$; **Fig. 2B**).

Four patients had evaluable paired metastatic tumor biopsies obtained at baseline and on-treatment (median duration of treatment 8 weeks prior to on-treatment biopsy). Time after the last ZEN-3694 + enzalutamide dosing prior to the biopsy ranged from 3.5 to 24 hours. The limited sample size precluded ability to perform statistical analyses of change in expression by dose level. However, on GSEAs, looking at changes between on-treatment versus pretreatment samples, there were strong indications of downregulation of expression of MYC and

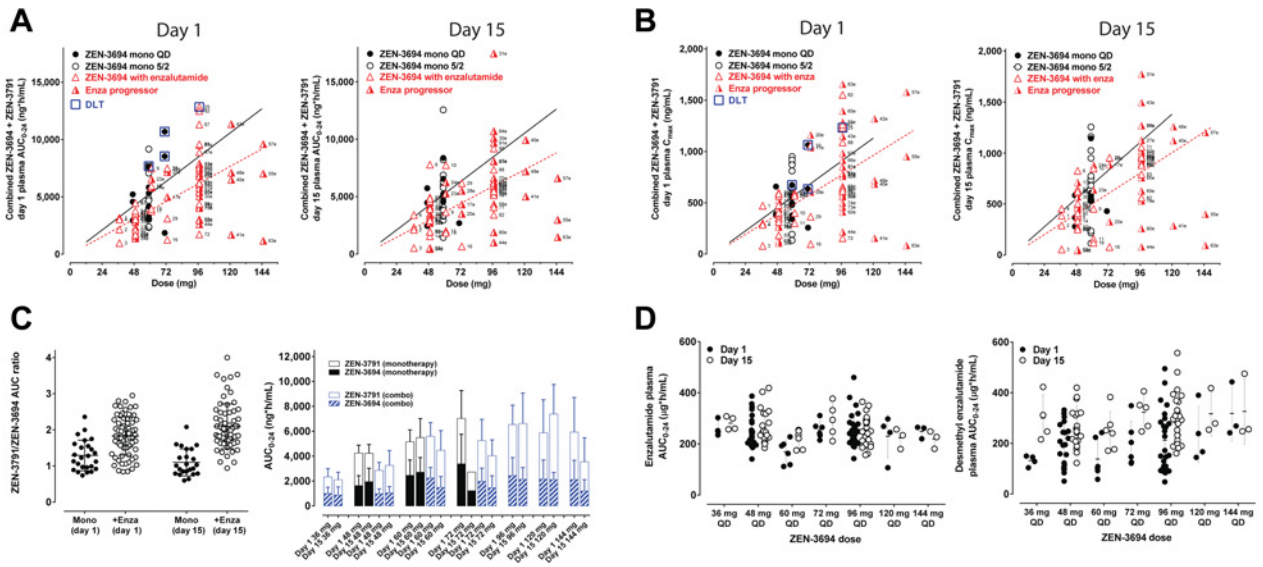


Figure 1.

Pharmacokinetics analyses. **A** and **B,** AUC from 0 to 24 hours (AUC_{0-24}) and maximum serum concentration, respectively, of ZEN-3694 + ZEN-3791 (first-generation active metabolite) serum concentration on day 1 and day 15 of cycle 1 (red triangles). Overlaid AUC_{0-24} data from the monotherapy (mono) trial of ZEN-3694 (23) are shown for dose levels 48 and 72 mg daily (black circles). **C,** Ratio of ZEN-3791 (first-generation active metabolite) versus ZEN-3694 (parent compound) from the prior monotherapy trial (23) and in combination with enzalutamide (enza) on day 1 and day 15 of cycle 1. **D,** Steady-state serum concentration of enzalutamide and desmethyl enzalutamide following 14 day lead-in of enzalutamide (day −14 to day −1), by ZEN-3694 dose level. QD, every day.

Published OnlineFirst July 21, 2020; DOI: 10.1158/1078-0432.CCR-20-1707

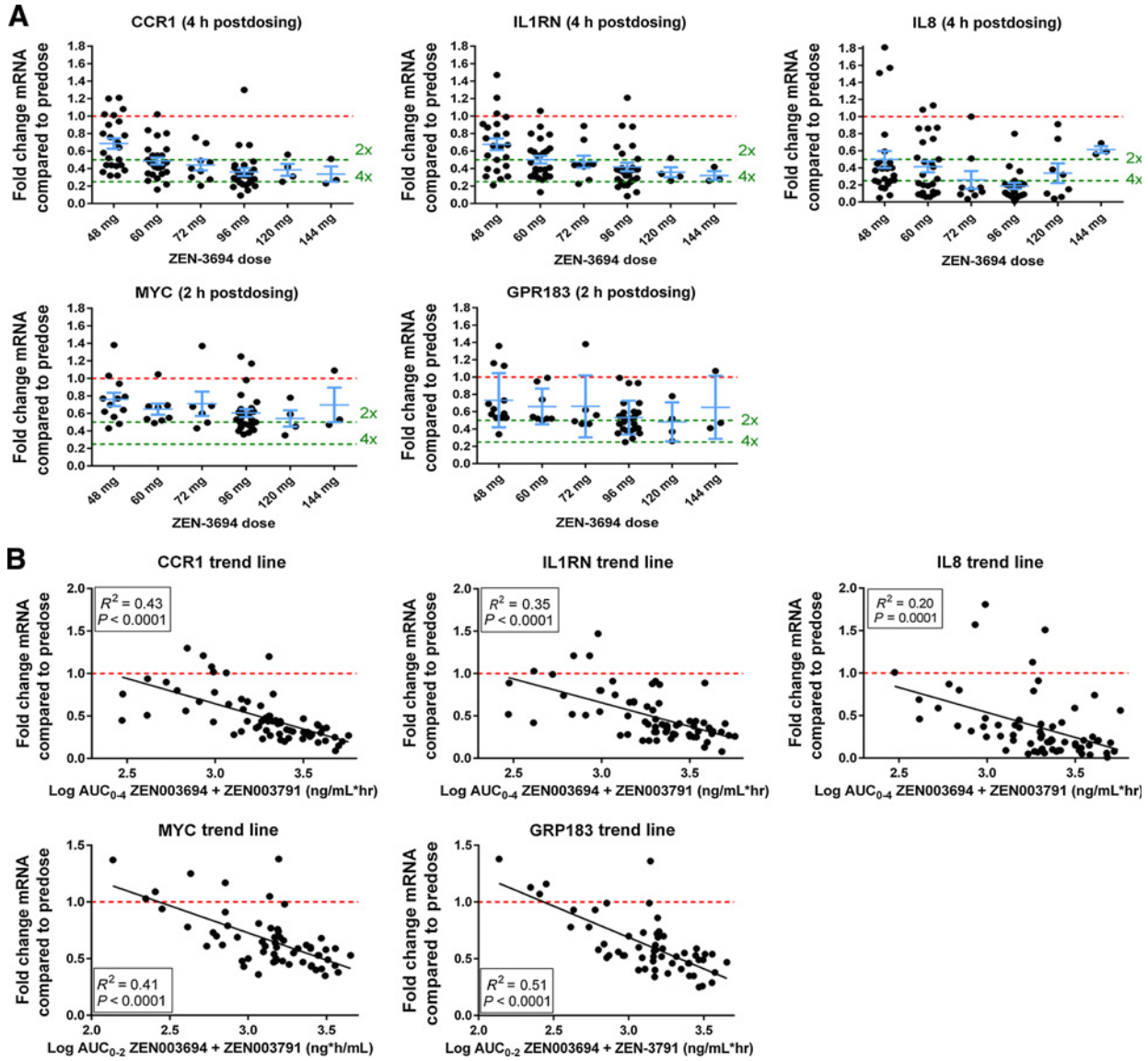


Figure 2.

Pharmacodynamics assessments. **A,** Fold-change from baseline in whole-blood RNA expression of BETi target genes *CCR1, IL1RN, IL8, MYC*, and *GPR183* by ZEN-3694 dose level. **B,** Correlation between fold change from baseline in whole-blood RNA expression of BETi target genes and AUC_{0-24} of ZEN-3694 + ZEN-3791 indicates strong pharmacokinetics–pharmacodynamics relationship. (*Continued on the following page.*)

AR signaling on-treatment compared with baseline biopsies, as well as downregulation of BET-dependent genes previously identified in LnCaP cells treated with the I-BET762 BETi (**Fig. 2C**; ref. 23).

Efficacy analyses

The median rPFS in the overall cohort was 9.0 months [95% confidence interval (CI), 4.6–12.9], with 7.8 months for patients that had progressed on abiraterone (95% CI, 4.9–10.6) and 10.1 months for patients that had progressed on enzalutamide (95% CI, 4.4–12.9; **Fig. 3A**). Composite median radiographic or clinical PFS was 5.5 months (95% CI, 4.0–7.8) in the overall cohort, and 5.5 months (95% CI, 4.4–7.8) and 5.1 months (95% CI, 3.2–10.1) in those with prior progression on abiraterone and enzalutamide, respectively (**Fig. 3B**). Thirteen (17%) and four (5%) patients remained on treatment for greater than 12 and 24 months without progression, respectively (**Fig. 3C**). In patients with radiographic progression at the time of study entry, the median rPFS was 7.8 months (95% CI, 4.4–10.6; **Fig. 3D**) and composite PFS was 4.8 months (95% CI, 3.5–7.7). An analysis of the subset of patients with primary resistance to prior first-line AR-targeted therapy ($N = 12$), defined by progression within 6 months of treatment initiation, demonstrated an on-treatment median rPFS of 10.6 months (95% CI, 7.5–not reached; **Fig. 3E**). Using a more stringent cutoff of primary resistance of progression within 16 weeks of prior first-line AR-targeted therapy ($N = 5$), likewise demonstrated prolonged median rPFS (median rPFS, 22.4 months; 95% CI, 7.8–not reached) and composite PFS (median

Published OnlineFirst July 21, 2020; DOI: 10.1158/1078-0432.CCR-20-1707

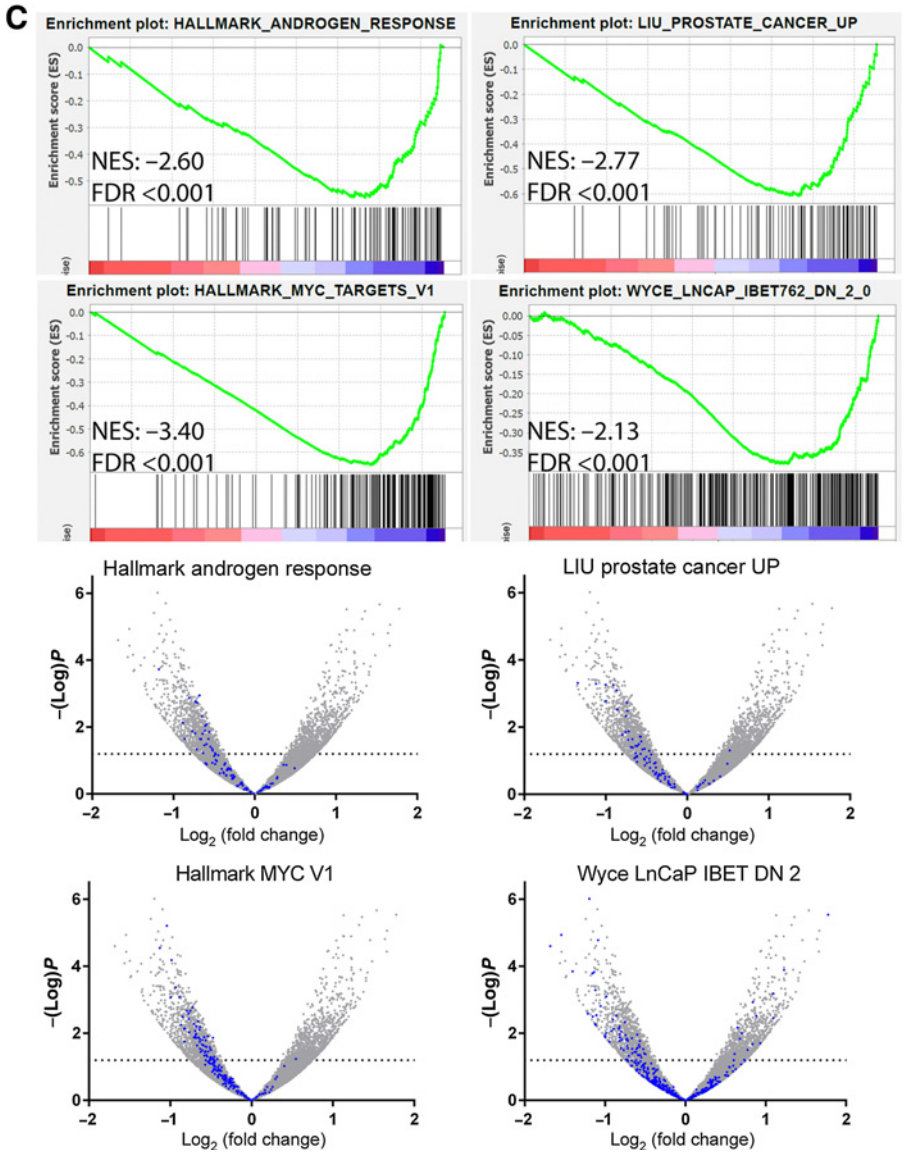


Figure 2.
(*Continued.*) **C,** GSEA of change from baseline in gene expression by RNA-seq in paired metastatic tumor biopsies. Downregulation of MYC signaling pathway was observed in on-treatment versus baseline tumor biopsy.

PFS, 10.6 months; 95% CI, 4.0, not reached) in this subset of patients (Supplementary Fig. S1A and S1B).

Of the four exceptional responders who remained on treatment for greater than 24 months duration, three had radiographic progression at study entry, two had progressed on prior enzalutamide, and one of the four patients experienced an objective radiographic response on enzalutamide + ZEN-3694 (Supplementary Table S2).

Six patients (8%) experienced a greater than 50% decline from baseline in serum PSA by PCWG2 criteria (PSA50 response), including two patients with prior progression on enzalutamide monotherapy. All PSA responses were confirmed on repeat measurement. Four patients (5.3%) experienced a greater than 90% decline in serum PSA from baseline on study treatment. PSA50 responses were sustained in the majority of cases with median duration of PSA50 response of 21.1 months (95% CI, 19.0–23.2). The median PSA PFS was 3.2 months (95% CI, 3.2–5.1) in the overall study cohort and 3.2 months (95% CI, 2.8–6.4) in those with PSA-only progression at study entry. There were no substantial differences with respect to rPFS, composite PFS, or PSA PFS noted between 48- and 96-mg dose-expansion cohorts.

In addition, in a subset of patients ($n = 21$), there was a transient increase of >2 ng/mL and 25% above baseline in serum PSA within the first 12 weeks of treatment with subsequent plateau in serum PSA level (Supplementary Fig. S2A). Patients with transient PSA increase as defined above appeared to derive sustained clinical benefit with median rPFS of 10.1 months (95% CI, 5.6–11.7). In contrast, patients whose serum PSA consistently rose beyond the 12-week timepoint ($n = 21$) experienced a median rPFS of 7.2 months (95% CI, 3.9–9.0; Supplementary Fig. S2B).

Predictors of prolonged clinical benefit with ZEN-3694 + enzalutamide

Exploratory analyses were performed with available genomic and transcriptional data from baseline tumor biopsies to evaluate association with subsequent time to progression (TTP) on treatment.

Published OnlineFirst July 21, 2020; DOI: 10.1158/1078-0432.CCR-20-1707

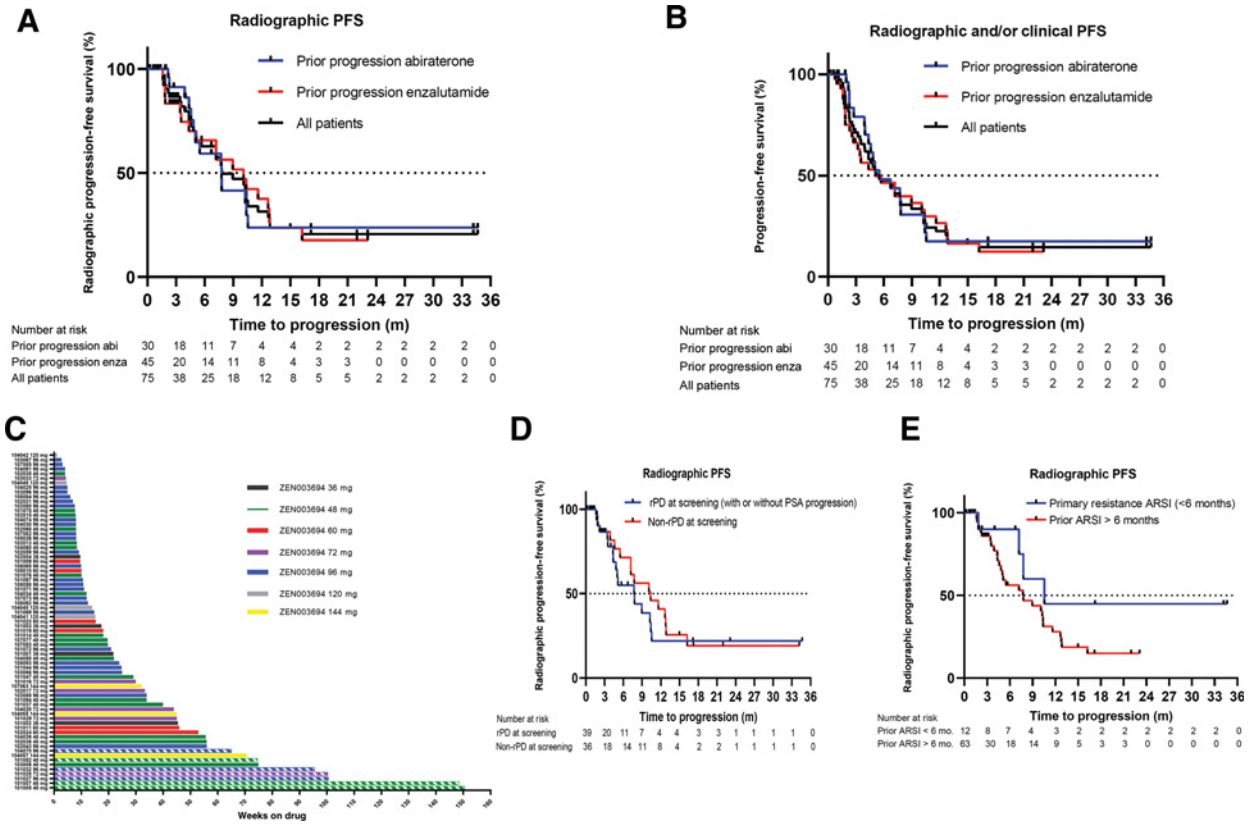


Figure 3.

rPFS and duration of treatment. **A,** Kaplan–Meier curve demonstrating rPFS by PCWG2 criteria in all evaluable study participants (black curve), patients with prior enzalutamide (enza) progression (blue curve), or prior abiraterone (abi) progression (green curve). **B,** Kaplan–Meier curve demonstrating composite PFS (time to first clinical or radiographic progression). **C,** Swimmer plot showing duration of treatment, with color labels by ZEN-3694 dose level (hashed line, treatment ongoing). **D** and **E,** Kaplan–Meier curves showing rPFS in subsets of patients with radiographic progression or primary resistance to prior ASI, respectively.

Interestingly, patients whose baseline metastatic tumor biopsies ($N = 13$) harbored lower canonical AR transcriptional activity, as assessed by 5-gene score (25) as well as the HALLMARK_ANDROGEN_RESPONSE signature, experienced a longer median TTP (median TTP 19 vs. 45 weeks; **Fig. 4A** and **B**). In support of the notion that tumors with lower canonical AR activity might be more responsive to BET inhibition, we observed a trend toward prolonged TTP among patients meeting clinical criteria for aggressive variant prostate cancer [e.g., low serum PSA <10 ng/mL with concomitant high disease burden (visceral metastases and/or >10 bone metastases); ref. 26]. The median TTP in patients with aggressive variant disease was 11.6 months (95% CI, 7.2–12.8) versus 5.5 months (95% CI, 2.3–10.6, $P = 0.24$) in those without aggressive variant clinical features at baseline (**Fig. 4C**).

Discussion

Our results demonstrate that the pan-BETi, ZEN-3694, has acceptable tolerability and encouraging preliminary efficacy data in combination with enzalutamide in patients with mCRPC. The median rPFS in the overall cohort was 9 months, and more than 10 months in those with prior progression on enzalutamide monotherapy. ZEN-3694 + enzalutamide treatment led to a two- to fourfold reduction in the expression of BET target genes including *MYC*, which was sustained throughout the 24-hour dosing interval. On the basis of the aggregate of the safety, efficacy, and evidence of robust downregulation of expression of BET-dependent target genes, ZEN-3694 at 96 mg daily has been selected as the recommended phase II dose to move forward in further clinical development in combination with enzalutamide. The clinical and pharmacodynamics data provide clinical evidence that BET inhibition may be able to abrogate resistance mechanisms and resensitize patients to ASIs.

The prolonged PFS observed in this study in relevant subsets, including those with radiographic progression at study entry, primary resistance to prior AR-targeted therapy, as well as those with prior progression on enzalutamide monotherapy, is consistent with an additive or potentially synergistic interaction between enzalutamide and ZEN-3694. The baseline characteristics of the study cohort are representative of other studies in the post-ASI mCRPC setting, including nearly one-third of patients with intermediate- or high-risk disease by Halabi prognostic model (27), and a quarter of whom required opioid analgesics at study entry. These features argue against the possibility of enrichment of better than average-risk group contributing significantly to the prolonged PFS observed on treatment. Taken together, the data support a randomized study to evaluate for the magnitude of benefit of ZEN-3694 in combination with enzalutamide.

With the caveat of cross-trial comparisons, the median PFS observed with ZEN-3694 + enzalutamide in this study compares favorably with outcomes observed with sequential AR targeting in

Published OnlineFirst July 21, 2020; DOI: 10.1158/1078-0432.CCR-20-1707

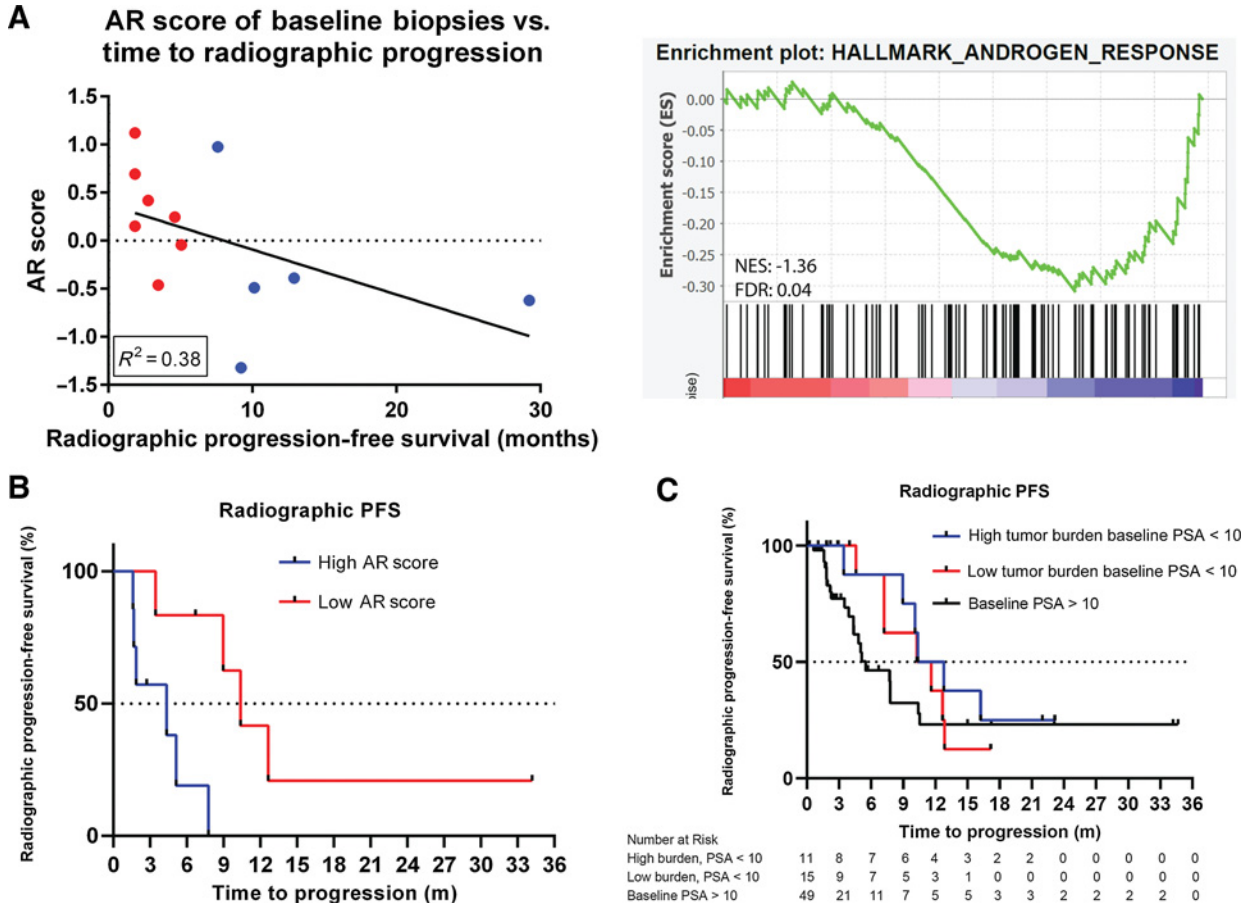


Figure 4.

AR signaling score and clinical outcomes. **A,** Lower AR activity level in baseline tumor biopsies is correlated with longer time on study ($R^2 = 0.38$) using either the 5-gene AR score (left) or the HALLMARK_ANDROGEN_RESPONSE (right) signatures. For the hallmark signature, baseline gene expression of biopsies from patients with radiographic progression prior to 24 weeks versus greater than 24 weeks were compared (FDR = 0.04). **B,** Kaplan–Meier curve showing significant increase in time to median rPFS in patients with lower AR signaling compared with patients with higher AR signaling score (median rPFS 10.4 months in tumors with low AR score versus 4.3 months in tumors with high AR activity). **C,** Patients with high tumor burden and lower baseline PSA levels (<10 ng/mL; blue curve) demonstrate longer PFS than patients with higher baseline PSA (>10 ng/mL) levels.

mCRPC with abiraterone followed by enzalutamide, or vice versa, in prior studies. In the prospective SWITCH phase II cross-over study, the median PFSs of second-line enzalutamide and abiraterone were 3.5 and 1.7 months, respectively (6). Similarly, median PFSs with second-line AR-targeting therapy have been less than 8 months in most retrospective series (9). Caution should be applied to overinterpretation of these cross-trial comparisons, and a randomized trial will be necessary to assess the individual contribution of ZEN-3694 added to enzalutamide in mCRPC.

The PSA50 response rate with the combination of ZEN-3694 plus enzalutamide was less than 10% in the study, and median PSA PFS was less than 4 months. Although this may reflect lack of additive benefit of ZEN-3694 in combination with enzalutamide, decline in serum PSA and PSA PFS may not be the best metrics to gauge efficacy of BETis including ZEN-3694. In fact, a subset of patients experienced transient early rises in serum PSA levels by week 8 of treatment, which were associated with longer TTP. In addition, tumors harboring lower AR activity at baseline appeared to derive more clinical benefit from treatment. Finally, those with low serum PSA in relation to metastatic disease burden, a clinical profile consistent with small-cell/neuroendocrine prostate cancer, may also have longer rPFS compared with those with higher baseline serum PSA levels. Although these observations are hypothesis generating and require prospective validation, it raises the intriguing possibility that BETis may restore dependency on AR signaling in tumors that are less reliant on AR prior to BETi or that BETi is blocking important AR-independent survival mechanisms, such as MYC, which have been shown to be critical for BETi effects in CRPC (13, 28, 29). AR-independent mCRPC is becoming more prevalent with the earlier application of ASIs, and is associated with shortened survival and unmet need to develop novel therapeutic approaches (14).

The acceptable toxicity profile of ZEN-3694 in combination with enzalutamide stands in contrast to the results observed with several other recent BETis reported in the literature, which have been limited by thrombocytopenia and GI toxicities (30, 31). In this study, there was substantially less thrombocytopenia observed. GI toxicities were not as prevalent or severe as prior studies and were manageable with early institution of antiemetics and dose reductions, if necessary. The reasons underlying the potentially more favorable toxicity profile observed in this study, as compared with other BETis, may relate to

patient factors such as excluding prior chemotherapy for mCRPC. Furthermore, it is possible that a pharmacokinetics interaction between ZEN-3694 and enzalutamide may have accelerated production of the first-generation active metabolite, ZEN-3791, which may have a more favorable toxicity profile. The differential toxicity compared with other BETis does not appear to relate to differences in potency, given the robust downregulation of BETi target genes observed in this study.

There were several limitations of the study, including the limited number of baseline and on-treatment paired biopsies, precluding the ability to identify a consistent predictive biomarker with a high degree of statistical confidence. The nonrandomized nature of the dose expansion portion of the study also limits our ability to draw definitive conclusions regarding the potential additive benefit of ZEN-3694, although evidence of contribution is provided by favorable comparison with contemporary controls from other studies as outlined above. AR-V7 splice variant status in circulating tumor cells, a validated resistance mechanism to AR-targeted therapy that may be downregulated with BETi treatment, was not reliably captured in this study in a sufficient number of patients to permit evaluation. Finally, there did not appear to be a relationship between dose level and efficacy outcomes, potentially related to fairly broad interpatient variability in ZEN-3694 exposure, limited sample size, and limited single-agent activity of ZEN-3694.

With the shift in application of potent AR-targeted therapy in earlier castration-sensitive settings, there is an increasing medical need to develop therapies that reverse therapeutic resistance and restore dependency on AR signaling. The preliminary data provided by the phase Ib/II study of ZEN-3694 plus enzalutamide provides strong justification to further investigate it in a prospective, randomized study.

Disclosure of Potential Conflicts of Interest

R. Aggarwal reports grants from Zenith Epigenetics during the conduct of the study, grants and personal fees from Janssen, Merck, and AstraZeneca, and personal fees from Dendreon and Clovis Oncology outside the submitted work. M.T. Schweizer reports grants from Zenith Epigenetics (research funds to institution) during the conduct of the study, Janssen (research funds to institution), AstraZeneca (research funds to institution), Madison Vaccines (research funds to institution), Pfizer (research funds to institution), and Hoffmann-La Roche (research funds to institution), and personal fees from Resverlogix (consulting fee) outside the submitted work. D.M. Nanus reports personal fees from Genentech Roche (DSMB) outside the submitted work. A. Pantuck reports grants from UCLA (clinical trial contract/grant) during the conduct of the study. E. Campeau reports personal fees and other from Zenith Epigenetics Ltd. (salary paid by Zenith Epigenetics Ltd.) during the conduct of the study and outside the submitted work, as well as has a patent for Combination Therapy for the Treatment of Prostate Cancer pending (all patent rights were transferred to Zenith Epigenetics Ltd.). M. Snyder reports personal fees and other from Zenith Epigenetics (employment) during the conduct of the study and outside the submitted work, as well as reports employment with Zenith Epigenetics. S. Lakhotia reports personal fees and other from Zenith Epigenetics (paid salaried employee of Zenith, lead clinical development for Zenith) during the conduct of the study and outside the submitted work, as well as has a patent on the combination of ZEN-3694 + enzalutamide for the treatment of prostate cancer, owned by Zenith Epigenetics. F.Y. Feng reports personal fees from Janssen Oncology (advisory board), Sanofi (advisory board), and Bayer (consultant), grants and other from Zenith Epigenetics (research funding from Zenith Epigenetics), other from PFS Genomics (founding member, ownership interests), and personal fees from Celgene (advisory board), Blue Earth Diagnostics (advisory board), Genentech (consultant), Myovant Sciences (consultant), Roivant Sciences (consultant), and Astellas Pharma (consultant) outside the submitted work. E.J. Small reports personal fees and other from Fortis Therapeutics (consulting and stock), personal fees from Harpoon Therapeutics (consulting), Janssen (consulting), BeiGene (consulting), Tolero (consulting), and Teon Therapeutics (consulting) outside the submitted work. W. Abida reports grants from Zenith Epigenetics (research funding to institution) during the conduct of the study, grants from Clovis Oncology (research funding to institution) and GlaxoSmithKline (research funding to institution) outside the submitted work, and personal fees from Clovis Oncology, Janssen Biotech, MORE Health, ORIC pharmaceuticals, and Daiichi Sankyo, grants from AstraZeneca (research funding to institution). J. Alumkal reports grants from Zenith Epigenetics (research support to institution), NCI (research support to institution) during the conduct of the study, and Aragon Pharmaceuticals (research support to institution), and Gilead Sciences (research support to institution) outside the submitted work, and grants and personal fees from Astellas (consulting fees and research support to institution) and Janssen Biotech (consulting fees and research support to institution) outside the submitted work. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

R. Aggarwal: Conceptualization, formal analysis, supervision, validation, investigation, visualization, methodology, writing-original draft, writing-review and editing. **M.T. Schweizer:** Conceptualization, formal analysis, supervision, validation, investigation, visualization, methodology, writing-original draft, writing-review and editing. **D.M. Nanus:** Formal analysis, supervision, validation, investigation, visualization, methodology, writing-original draft, writing-review and editing. **A. Pantuck:** Conceptualization, formal analysis, supervision, validation, investigation, visualization, methodology, writing-original draft, writing-review and editing. **E. Heath:** Conceptualization, data curation, software, supervision, validation, investigation, visualization, methodology, writing-original draft, writing-review and editing. **E. Campeau:** Data curation, software, formal analysis, visualization, writing-original draft, writing-review and editing. **S. Attwell:** Conceptualization, data curation, software, formal analysis, supervision, investigation, methodology, writing-original draft, project administration, writing-review and editing. **K. Norek:** Conceptualization, software, supervision, validation, investigation, visualization, methodology. **M. Snyder:** Conceptualization, resources, data curation, software, formal analysis, validation, visualization, methodology, writing-original draft, project administration, writing-review and editing. **L. Bauman:** Conceptualization, resources, data curation, software, formal analysis, supervision, validation, visualization, methodology, writing-original draft, writing-review and editing. **S. Lakhotia:** Conceptualization, resources, supervision, funding acquisition, writing-review and editing. **F.Y. Feng:** Conceptualization, data curation, software, supervision, validation, investigation, visualization, methodology, writing-original draft, writing-review and editing. **E.J. Small:** Conceptualization, software, formal analysis, funding acquisition, validation, investigation, visualization, methodology, writing-original draft, writing-review and editing. **W. Abida:** Conceptualization, data curation, software, formal analysis, supervision, validation, investigation, visualization, methodology, writing-original draft, writing-review and editing. **J. Alumkal:** Conceptualization, data curation, software, formal analysis, supervision, funding acquisition, validation, investigation, visualization, methodology, writing-original draft, writing-review and editing.

Acknowledgments

The financial support and study drug supply was provided by Zenith Epigenetics. R. Aggarwal received funding from the Prostate Cancer Foundation and the Department of Defense Prostate Cancer Research Program grant W81XWH1820039. W. Abida was funded by NIH NCI Cancer Center Support grant (P30CA008748) and Prostate Cancer SPORE (P50CA092629), the Department of Defense Physician Research Award W81XWH-17-1-0124, and the Prostate Cancer Foundation. J. Alumkal received funding from NCI R01 CA251245, the Pacific Northwest Prostate Cancer SPORE (NCI P50 CA097186), and the Michigan Prostate SPORE (NCI P50 CA186786). J. Alumkal is currently employed by the University of Michigan. F.Y. Feng received funding from the Prostate Cancer Foundation.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received May 4, 2020; revised June 24, 2020; accepted July 17, 2020; published first July 21, 2020.

Published OnlineFirst July 21, 2020; DOI: 10.1158/1078-0432.CCR-20-1707

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70:7–30.
2. Ryan CJ, Smith MR, de Bono JS, Molina A, Logothetis CJ, de Souza P, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 2013;368:138–48.
3. Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014;371:424–33.
4. Fizazi K, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev BY, et al. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial. Lancet Oncol 2019;20:686–70.
5. Chi KN, Agarwal N, Bjartell A, Chung BHa, Pereira de Santana Gomes AJ, Given R, et al. Apalutamide for metastatic castration-sensitive prostate cancer. N Engl J Med 2019;381:13–24.
6. Khalaf DJ, Annala M, Taavitsainen S, Finch DL, Oja C, Vergidis J, et al. Optimal sequencing of enzalutamide and abiraterone acetate plus prednisone in metastatic castration-resistant prostate cancer: a multicentre, randomised, open-label, phase 2, crossover trial. Lancet Oncol 2019;20:1730–9.
7. Attard G, Borre M, Gurney H, Loriot Y, Andresen-Daniil C, Kalleda R, et al. Abiraterone alone or in combination with enzalutamide in metastatic castration-resistant prostate cancer with rising prostate-specific antigen during enzalutamide treatment. J Clin Oncol 2018;36:2639–46.
8. de Bono JS, Chowdhury S, Feyerabend S, Elliott T, Grande E, Melhem-Bertrandt A, et al. Antitumour activity and safety of enzalutamide in patients with metastatic castration-resistant prostate cancer previously treated with abiraterone acetate plus prednisone for ≥ 24 weeks in Europe. Eur Urol 2018;74:37–45.
9. Mori K, Miura N, Mostafaei H, Quhal F, Sari Motlagh R, Pradere B, et al. Sequential therapy of abiraterone and enzalutamide in castration-resistant prostate cancer: a systematic review and meta-analysis. Prostate Cancer Prostatic Dis 2020 Mar 9 [Epub ahead of print].
10. Morris MJ, Heller G, Bryce AH, Armstrong AJ, Beltran H, Hahn OM, et al. Alliance A031201: a phase III trial of enzalutamide versus enzalutamide, abiraterone, and prednisone for metastatic castration resistant prostate cancer. J Clin Oncol 2019;37:5008.
11. Antonarakis ES, Lu C, Wang H, Luber B, Nakazawa M, Roeser JC, et al. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. N Engl J Med 2014;371:1028–38.
12. Montgomery RB, Mostaghel EA, Vessella R, Hess DL, Kalhorn TF, Higano CS, et al. Maintenance of intratumoral androgens in metastatic prostate cancer: a mechanism for castration-resistant tumor growth. Cancer Res 2008;68:4447–54.
13. Quigley DA, Dang HaX, Zhao SG, Lloyd P, Aggarwal R, Alumkal JJ, et al. Genomic hallmarks and structural variation in metastatic prostate cancer. Cell 2018;175:889.
14. Aggarwal R, Huang J, Alumkal JJ, Zhang Li, Feng FY, Thomas GV, et al. Clinical and genomic characterization of treatment-emergent small-cell neuroendocrine prostate cancer: a multi-institutional prospective study. J Clin Oncol 2018;36:2492–503.
15. Arora VK, Schenkein E, Murali R, Subudhi SK, Wongvipat J, Balbas MD, et al. Glucocorticoid receptor confers resistance to antiandrogens by bypassing androgen receptor blockade. Cell 2013;155:1309–22.
16. Shah N, Wang P, Wongvipat J, Karthaus WR, Abida W, Armenia J, et al. Regulation of the glucocorticoid receptor via a BET-dependent enhancer drives antiandrogen resistance in prostate cancer. Elife 2017;6:e27861.
17. Mertz JA, Conery AR, Bryant BM, Sandy P, Balasubramanian S, Mele DA, et al. Targeting MYC dependence in cancer by inhibiting BET bromodomains. Proc Natl Acad Sci U S A 2011;108:16669–74.
18. Attwell S, Jahagirdar R, Norek K, Calosing C, Tsujikawa L, Kharenko OA, et al. Preclinical characterization of ZEN-3694, a novel BET bromodomain inhibitor entering phase I studies for metastatic castration-resistant prostate cancer (mCRPC) [abstract]. In: Proceedings of the 107th Annual Meeting of the American Association for Cancer Research; 2016 Apr 16–20; New Orleans, LA. Philadelphia (PA): AACR; 2016. Abstract nr LB-207.
19. Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 2008;26:1148–59.
20. Tsujikawa L, Norek K, Calosing C, Attwell S, Gilham D, Sharma N, et al. Abstract LB-038: preclinical development and clinical validation of a whole blood pharmacodynamic marker assay for the BET bromodomain inhibitor ZEN-3694 in metastatic castration-resistant prostate cancer patients. Cancer Res 2017;77:LB–038.
21. The Molecular Signatures Database v7.0 (Broad Institute). https://www.gsea-msigdb.org/gsea/msigdb/index.jsp.
22. Liu P, Ramachandran S, Ali Seyed M, Scharer CD, Laycock N, Dalton WB, et al. Sex-determining region Y box 4 is a transforming oncogene in human prostate cancer cells. Cancer Res 2006;66:4011–9.
23. Wyce A, Degenhardt Y, Bai Y, Le B, Korenchuk S, Crouthamel M-C, et al. Inhibition of BET bromodomain proteins as a therapeutic approach in prostate cancer. Oncotarget 2013;4:2419–29.
24. Aggarwal R, Abida W, Schweizer M, Pantuck A, Nanus D, Heath E, et al. A phase Ib/IIa study of the BET bromodomain inhibitor ZEN-3694 in combination with enzalutamide in patients with metastatic castration-resistant prostate cancer (mCRPC) [abstract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2019; 2019 Mar 29–Apr 3; Atlanta, GA. Philadelphia (PA): AACR; 2019. Abstract nr CT095.
25. Miao L, Yang L, Li R, Rodrigues DN, Crespo M, Hsieh JT, et al. Disrupting androgen receptor signaling induces snail-mediated epithelial-mesenchymal plasticity in prostate cancer. Cancer Res 2017;77:3101–12.
26. Corn PG, Heath EI, Zurita A, Ramesh N, Xiao L, Sei E, et al. Cabazitaxel plus carboplatin for the treatment of men with metastatic castration-resistant prostate cancers: a randomised, open-label, phase 1–2 trial. Lancet Oncol 2019;20:1432–43.
27. Halabi S, Lin C-Y, Kelly WK, Fizazi KS, Moul JW, Kaplan EB, et al. Updated prognostic model for predicting overall survival in first-line chemotherapy for patients with metastatic castration-resistant prostate cancer. J Clin Oncol 2014;32:671–7.
28. Coleman DJ, Gao L, Schwartzman J, Korkola JE, Sampson D, Derrick DS, et al. Maintenance of MYC expression promotes do novo resistance to BET bromodomain inhibition in castration-resistant prostate cancer. Sci Rep 2019;9:3823.
29. Coleman DJ, Gao L, King CJ, Schwartzman J, Urrutia J, Sehrawat A, et al. BET bromodomain inhibition blocks the function of a critical AR-independent master regulatory network in lethal prostate cancer. Oncogene 2019;38:5658–69.
30. Piha-Paul S, Hann CL, French CA, Cousin S, Braña I, Cassier PA, et al. Phase 1 study of molibresib (GSK525762), a bromodomain and extra-terminal domain protein inhibitor, in NUT carcinoma and other solid tumors. JNCI Cancer Spectr 2019;4:pkz093.
31. Patel MR, Garcia-Manero G, Paquette R, Dinner S, Donnellan WB, Grunwald MR, et al. Phase 1 dose escalation and expansion study to determine safety, tolerability, pharmacokinetics, and pharmacodynamics of the BET inhibitor FT-1101 as a single agent in patients with relapsed or refractory hematologic malignancies. Blood 2019;134:3907.

AACR American Association for Cancer Research

Clinical Cancer Research

A Phase Ib/IIa Study of the Pan-BET Inhibitor ZEN-3694 in Combination with Enzalutamide in Patients with Metastatic Castration-resistant Prostate Cancer

Rahul R. Aggarwal, Michael T. Schweizer, David M. Nanus, et al.

Clin Cancer Res Published OnlineFirst July 21, 2020.

special articles

Implementation of Germline Testing for Prostate Cancer: Philadelphia Prostate Cancer Consensus Conference 2019

Veda N. Giri, MD[1,2,3]; Karen E. Knudsen, MBA, PhD[3]; William K. Kelly, DO[1]; Heather H. Cheng, MD, PhD[4]; Kathleen A. Cooney, MD[5]; Michael S. Cookson, MD[6]; William Dahut, MD[7]; Scott Weissman, MS[8]; Howard R. Soule, PhD[9]; Daniel P. Petrylak, MD[10]; Adam P. Dicker, MD, PhD[11]; Saud H. AlDubayan, MD[12]; Amanda E. Toland, PhD[13]; Colin C. Pritchard, MD, PhD[14]; Curtis A. Pettaway, MD[15]; Mary B. Daly, MD, PhD[16]; James L. Mohler, MD[17]; J. Kellogg Parsons, MD[18]; Peter R. Carroll, MD, MPH[19]; Robert Pilarski, MS, MSW[20]; Amie Blanco, MS[21]; Ashley Woodson, MS[15]; Alanna Rahm, PhD[22]; Mary-Ellen Taplin, MD[12]; Thomas J. Polascik, MD[23]; Brian T. Helfand, MD, PhD[24]; Colette Hyatt, MS[25]; Alicia K. Morgans, MD, MPH[26]; Felix Feng, MD[27]; Michael Mullane, MD[28]; Jacqueline Powers, MS[29]; Raoul Concepcion, MD[30]; Daniel W. Lin, MD[31]; Richard Wender, MD[32]; James Ryan Mark, MD[2]; Anthony Costello, MBBS[33]; Arthur L. Burnett, MD, MBA[34]; Oliver Sartor, MD[35]; William B. Isaacs, PhD[36]; Jianfeng Xu, MD, DrPH[24]; Jeffrey Weitzel, MD[37]; Gerald L. Andriole, MD[38]; Himisha Beltran, MD[39]; Alberto Briganti, MD, PhD[40]; Lindsey Byrne, MS[41]; Anne Calvaresi, DNP[2]; Thenappan Chandrasekar, MD[2]; David Y. T. Chen, MD[16]; Robert B. Den, MD[11]; Albert Dobi, PhD[42]; E. David Crawford, MD[43]; James Eastham, MD[44]; Scott Eggener, MD[45]; Matthew L. Freedman, MD[39]; Marc Garnick, MD[46]; Patrick T. Gomella, MD, MPH[47]; Nathan Handley, MD, MBA[1]; Mark D. Hurwitz, MD[11]; Joseph Izes, MD, MS[2]; R. Jeffrey Karnes, MD[48]; Costas Lallas, MD[2]; Lucia Languino, PhD[3]; Stacy Loeb, MD, MSc[49]; Ana Maria Lopez, MD, MPH[1]; Kevin R. Loughlin, MD, MBA[50]; Grace Lu-Yao, PhD, MPH[1]; S. Bruce Malkowicz, MD[51]; Mark Mann, MD[2]; Patrick Mille, MD[1]; Martin M. Miner, MD[52]; Todd Morgan, MD[53]; Jose Moreno, MD[54]; Lorelei Mucci, ScD, MPH[55]; Ronald E. Myers, DSW, PhD[1]; Sarah M. Nielsen, MS[45]; Brock O'Neil, MD[56]; Wayne Pinover, DO[57]; Peter Pinto, MD[47]; Wendy Poage, MHA[58]; Ganesh V. Raj, MD, PhD[59]; Timothy R. Rebbeck, PhD[55]; Charles Ryan, MD[60]; Howard Sandler, MD, MS[61]; Matthew Schiewer, PhD[3]; E. Michael D. Scott, BSc[62]; Brittany Szymaniak, PhD, MS[63]; William Tester, MD[1]; Edouard J. Trabulsi, MD[2]; Neha Vapiwala, MD[51]; Evan Y. Yu, MD[64]; Charnita Zeigler-Johnson, PhD, MPH[1]; and Leonard G. Gomella, MD[2]

ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on March 27, 2020 and published at ascopubs.org/journal/jco on June 9, 2020: DOI https://doi.org/10.1200/JCO.20.00046

abstract

PURPOSE Germline testing (GT) is a central feature of prostate cancer (PCA) treatment, management, and hereditary cancer assessment. Critical needs include optimized multigene testing strategies that incorporate evolving genetic data, consistency in GT indications and management, and alternate genetic evaluation models that address the rising demand for genetic services.

METHODS A multidisciplinary consensus conference that included experts, stakeholders, and national organization leaders was convened in response to current practice challenges and to develop a genetic implementation framework. Evidence review informed questions using the modified Delphi model. The final framework included criteria with strong (> 75%) agreement (Recommend) or moderate (50% to 74%) agreement (Consider).

RESULTS Large germline panels and somatic testing were recommended for metastatic PCA. Reflex testing—initial testing of priority genes followed by expanded testing—was suggested for multiple scenarios. Metastatic disease or family history suggestive of hereditary PCA was recommended for GT. Additional family history and pathologic criteria garnered moderate consensus. Priority genes to test for metastatic disease treatment included *BRCA2, BRCA1,* and mismatch repair genes, with broader testing, such as *ATM*, for clinical trial eligibility. *BRCA2* was recommended for active surveillance discussions. Screening starting at age 40 years or 10 years before the youngest PCA diagnosis in a family was recommended for *BRCA2* carriers, with consideration in *HOXB13, BRCA1, ATM*, and mismatch repair carriers. Collaborative (point-of-care) evaluation models between health care and genetic providers was endorsed to address the genetic counseling shortage. The genetic evaluation framework included optimal pretest informed consent, post-test discussion, cascade testing, and technology-based approaches.

CONCLUSION This multidisciplinary, consensus-driven PCA genetic implementation framework provides novel guidance to clinicians and patients tailored to the precision era. Multiple research, education, and policy needs remain of importance.

J Clin Oncol 38:2798-2811. © 2020 by American Society of Clinical Oncology

INTRODUCTION

The role of germline testing (GT) for prostate cancer (PCA) has increased, with growing precision treatment implications and expanded testing options.[1,2] A primary driver for GT is now precision therapy for metastatic disease where genetic results inform options and strategies for targeted treatment, therapeutic planning, and clinical trials.[1-4] Approximately 12% to 17% of men with metastatic PCA harbor germline mutations, primarily in DNA repair genes, such as

BRCA2, CHEK2, BRCA1, ATM, PALB2, and the DNA mismatch repair (MMR) genes,[5] which are increasingly informing options for poly (ADP-ribose) polymerase (PARP) inhibitors, immune checkpoint inhibitors, platinum chemotherapy, and clinical trials.[1-4,6] In early-stage disease, emerging data suggest that men with germline *BRCA2* mutations, and possibly *ATM* mutations, have higher rates of upgrading of prostate biopsies while on active surveillance (AS).[7] GT results are considered increasingly in PCA early detection discussions, particularly for men with *BRCA2* mutations for which data support higher rates of PCA detection, younger age at diagnosis, and more clinically significant disease.[8-10] Many of the genes that are important for PCA therapy, management, and early detection are associated with hereditary cancer syndromes.[11] Pathogenic variants in *BRCA1* and *BRCA2* are associated with hereditary breast and ovarian cancer (HBOC). DNA MMR genes—*MLH1, MSH2, PMS2, MSH6,* and *EPCAM*—are associated with Lynch syndrome.[11-16] These and other hereditary cancer syndromes confer risks for multiple cancers that must be addressed for men and their kindred.[8,16]

As PCA GT has increased, new practice and implementation challenges have emerged in three major areas: expanded options for multigene panels, with a resultant lack of clarity regarding optimized panel use and priority genes to test; variability in guidelines regarding GT indications and genetically based management that incorporates emerging data; and a shortage of genetic services.[1,17-21] Testing options have expanded rapidly, which include focused, guideline-based, comprehensive, and reflex panels.[17,18] Panels include genes with strong, limited, and unknown risk for PCA and that yet confer risks for multiple cancers.[18] There is a need for clarity on panel choice and priority genes to test in men with metastatic PCA, nonmetastatic PCA, and men at high risk for PCA that balances the benefits of expanded testing (eg, identifying actionable mutations) with considerations (eg, higher rates of variants of uncertain significance [VUS]).[3,8,10]

Uniform guidance is also needed regarding GT indications and genetically based PCA management that incorporates rapidly emerging, sometimes conflicting, data. Current National Comprehensive Cancer Network (NCCN) guidelines have variability regarding GT on the basis of pathologic—stage and Gleason/Grade Group—and family history (FH) criteria.[3,8,9] Management guidance is also needed in multiple areas with consideration of gene-specific outcomes, such as treatment of metastatic disease with variable responses by DNA repair mutations[1-4,6]; AS discussions that consider strong data for *BRCA2*, but limited data for *BRCA1* and *ATM*[7]; and broader consideration of genes for PCA early detection.[1,2,11] In particular, strategies for PCA early detection need clarification regarding age to begin screening on the basis of genetic status.[8,9]

Furthermore, the rising need for PCA GT has created a critical shortage of genetic counseling (GC) services.[1,19] Health care providers, such as oncologists and urologists, increasingly are ordering PCA GT to expedite testing for management.[20,21] Concerns include limited guidance on optimal pretest informed consent, optimal panel testing strategies for comprehensive genetic evaluation, inclusion of personal history and FH, and balancing timely GT with appropriate referral to GC to address patient and family needs.[1,20,21] As referral of all men to GC for PCA GT is not sustainable, health care and genetic providers need implementation strategies that incorporate alternate genetic evaluation models for the timely and responsible delivery of PCA GT for men and their families.[1,19]

The 2019 Philadelphia Prostate Cancer Consensus Conference was convened to address challenges in PCA germline evaluation and implementation with attention to evolving genetic and precision medicine data. This meeting was a follow-up to the 2017 Philadelphia Consensus Conference, which focused on the role of GT for inherited PCA risk.[18] The 2019 conference had the following 3 goals: to define optimal GT strategies that incorporate expansion of panel testing options and evolving genetic data, to propose consistent PCA GT indications and management, and to propose alternate genetic evaluation models to address the GC shortage. An expert, consensus-driven genetic implementation framework was developed for health care and genetic providers to streamline GT for PCA in the precision medicine era.

METHODS

Overarching Questions Addressing Implementation Gaps

The following questions were primary drivers of the conceptual framework:

1. Which men should be considered for germline PCA genetic testing?
2. Which panels should be considered and which genes should be prioritized for testing?
3. What PCA-specific recommendations should be considered on the basis of genetic results?
4. What is optimal informed consent for PCA GT?
5. What collaborative strategies may facilitate PCA genetic evaluation between health care and genetic providers?
6. What post-test disclosure strategies are most appropriate on the basis of genetic results?
7. What barriers must be addressed to enhance PCA GT?

Consensus Conference Participants

The Consensus Conference included 97 participants spanning the fields of urology, medical oncology, radiation oncology, clinical genetics, genetic counseling, primary care, pathology, implementation science, population science, epidemiology, and basic science. Patient stakeholders and advocates were active participants. Members of several national organizations, which included NCCN representatives, also participated. Academic and

community practices were represented, and panelists were from multiple regions of the United States, as well as Europe and Australia. The final voting panel included 76 participants (Table 1).

Consensus Process

The modified Delphi model was followed that incorporated elements of the Delphi process as previously published.[18,22,23] Literature was provided to panel members before the meeting. Multiple expert presentations summarizing evidence relevant to genetic implementation were delivered. Evidence review is summarized in the Data Supplement.

Evidence Review

Thematic topics included: genetic contribution to PCA risk/aggressiveness[24-54]; germline mutations by PCA clinical and molecular characteristics[5,55-66]; PCA clinical multigene testing data[60,61,67]; germline mutations in diverse populations[5,24,30,49,61,68-74]; PCA genetic testing capabilities and considerations[17,75-81] (Fig 1); implementation of GC[1,3,8,9,17,76,82-93]; NCCN PCA genetic testing guidelines and current variability[3,8,9]; GT for PCA precision medicine in the metastatic setting[2,4,6,56,58,94-99]; germline implications for AS of early-stage PCA[7,35,99,100,101]; and germline implications for PCA early detection.[8-10,102] Table 2 provides a summary of genetic data for PCA risk and aggressiveness. Full evidence summary is provided in the Data Supplement.

Strength of Consensus

Votes were cast anonymously using a Web-based polling platform. Strength of consensus was ≥ 75% agreement for strong consensus, 50% to 74% agreement for moderate consensus, and < 50% agreement for lack of consensus.[22,23]

Development of PCA Genetic Evaluation and Management Framework

A conceptual framework for PCA genetic evaluation and management was developed (Fig 2). Criteria that achieved strong consensus were designated as "Recommend" and those with moderate consensus were designated as "Consider" in the final framework.

RESULTS

Key premises

The following are guiding principles for clinical genetic evaluation:

Premises based on prior literature and Consensus Conference expert guidance:

- In-person GC is a gold standard of genetics practice.[2,76,82-84]
- Patients' psychosocial needs or preferences should dictate the mode of counseling.[1,82-84]
- Full FH is important to collect during the genetic evaluation process:[1,82-84]

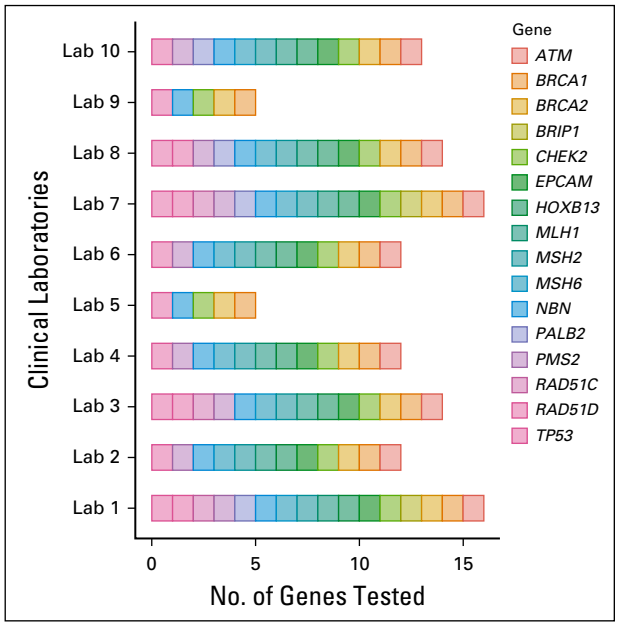


FIG 1. Variability in prostate cancer–specific multigene panels. Genetic testing registry: As of August 2019. Available at: https://www.ncbi.nlm.gov/gtr/. Courtesy of Saud AlDubayan, MD.

Premises based on consensus voting:

- Men should engage in informed decision making for genetic testing (Recommend).
- Building collaborations between health care and genetics providers is important for optimal genetic evaluation (Recommend).

1. Which Men Should Be Considered for Germline PCA Genetic Testing?

Gaps addressed. NCCN guidelines (NCCN Prostate Version 4.2019 and NCCN Breast/Ovary Version 3.2019) at the time of the 2019 Consensus meeting had varying indications for PCA GT.[3,8] Data regarding clinical, pathologic, and FH features were summarized (Data Supplement).

Criteria for testing. Any one of the following criteria may prompt GT:

- **Men with metastatic PCA** (castration resistant or castration sensitive; Recommend).
- **Men with nonmetastatic PCA**—one of the following:
  - Ashkenazi Jewish ancestry (Consider).
  - Advanced disease (T3a or higher; Consider).
  - Intraductal/ductal pathology (Consider).
  - Grade Group 4 (Gleason sum 8) or above (Consider).
- **FH criteria**:
  - **PCA FH criteria**:
    - Men with one brother or father or two or more male relatives with one of the following:
      - Diagnosed with PCA at age < 60 years (Recommend).

- Any of whom died of PCA (Recommend).
- Any of whom had metastatic PCA (Recommend).

○ **FH of other cancers**:

- Two or more cancers in HBOC or Lynch spectrum in any relatives on the same side of the family (especially if diagnosed at age < 50 years; Consider).

Additional considerations. FH consistent with hereditary PCA achieved a strong recommendation for GT. Additional FH criteria were expanded to consider 2 or more cancers in the HBOC or Lynch spectrum to account for limitations in self-reported FH. Genes corresponding to specific cancers are listed in Table 2. Of note, an unremarkable FH does not necessarily negate consideration of GT, particularly for treatment decisions in the metastatic setting.

All pathologic criteria achieved moderate agreement. Universal screening for Lynch syndrome in PCA is not current practice; however, if immunohistochemistry is performed on a prostate specimen revealing loss of the DNA MMR genes, and particularly MSH2, the recommendation is to proceed with GT to determine if the patient has Lynch syndrome given the significant cancer risks and potential treatment implications. Panelists noted that many centers do not report intraductal/ductal pathology or immunohistochemistry for Lynch syndrome markers, which must be addressed with pathologists.

Although multiple unique questions were posed specifically regarding GT for African American men, none met consensus agreement as a result of limited data. Until additional research is completed, testing guidelines as described herein should be applied in under-represented populations.

2. Which Panels Should Be Considered and Which Genes Should Be Prioritized for Testing?

Gaps addressed. Guidance on the use of various gene panels adapted to clinical scenarios is needed given the rapid expansion of panel options and the inclusion of genes with limited association to PCA risk or PCA treatment implications (Fig 1). Furthermore, NCCN guidelines vary regarding genes to test,[3,8] necessitating consensus prioritization of genes for testing (Data Supplement).

Panels considered. Focused—guidelines-based—panels (approximately 5 to 6 genes), PCA-specific panels (approximately 10 to 15 genes), comprehensive cancer panels (approximately 80 genes), and reflex panels (initial set of genes tested followed by broad gene testing) were considered. Benefits and limitations of various panels were also considered (Data Supplement).

Genes considered. *BRCA1*, *BRCA2*, *HOXB13*, *CHEK2*, *ATM*, *NBN*, *MSH2*, *MSH6*, *MLH1*, *PMS2*, *PALB2*, *BRIP1*, *TP53*, and Fanconi anemia genes were considered.

TABLE 1. Characteristics of Voting Consensus Participants

Participant Characteristic	No. (%)
Primary area of specialty/work (combination of academic and community settings)	
Urology	29 (38)
Medical oncology	13 (17)
Genetic counseling/implementation science	10 (13)
Radiation oncology	5 (7)
Primary care, pathology, and other	9 (12)
Population science/epidemiology	4 (5)
Patient/patient advocate	6 (8)
Geographic region of practice or work	
Northeast United States	26 (34)
Mid-Atlantic United States	14 (18)
Southeast United States	4 (5)
Midwest United States	15 (20)
Southcentral United States	4 (5)
Northwest United States	6 (8)
Southwest United States	3 (4)
Europe, Australia, and Other	4 (5)
Type of region of work	
Urban	55 (71)
Suburban	15 (19)
Rural	2 (3)
Other	5 (6)

TABLE 2. Genetic Contribution to PCA Risk, Aggressiveness, and Proposed Clinical Implications

Gene	Strength of Association for PCA Susceptibility[a]	Risk for Aggressive Disease[a]	Prevalence in Metastatic PCA[b]	Testing for Hereditary Cancer Syndromes and Other Associated Cancers Based on Personal History or FH	Cancer Screening Guidelines for Non-PCAs	PCA-Specific Clinical Impact of Germline Testing: Consensus Conference Summary			
						Implications for PCA Early Detection/PCA Risk Assessment	Implications for AS Decision Making	Metastatic Treatment Options	Clinical Trial Options
ATM	+	++	++	Breast, pancreas	x	+/++	+	++	+++
BRCA1	++	+/−	+	HBOC syndrome; breast (male and female), ovarian, pancreas, melanoma	x	++		+++	+++
BRCA2	+++	+++	+++	HBOC syndrome; breast (male and female), ovarian, pancreas, melanoma	x	+++	++	+++	+++
HOXB13	+++	–	–	Hereditary PCA		++			
CHEK2	++	+	++	Breast, colon	x				++
MSH2/ MSH6	++	+	+	Lynch syndrome; colorectal, ovarian, uterine, gastric, small bowel, pancreas, upper tract urothelial, kidney, sebaceous carcinoma	x	++		++	+++
MLH1/ PMS2	+	+/−	+	Lynch syndrome; colorectal, ovarian, uterine, gastric, small bowel, pancreas, upper tract urothelial, kidney, sebaceous carcinoma	x	+		++	+++
NBN	+/−	+/−	+	Breast	x				+
PALB2	–	+	+	Breast, pancreas	x				++
RAD51C-D; BRIP1; Fanconi anemia genes	–	–	+	ovarian *(RAD51C/D, BRIP1)*	x				++

Abbreviations: AS, active surveillance; FH, family history; HBOC, hereditary breast and ovarian cancer; PCA, prostate cancer.

[a]Evidence from case-control, familial, cohort, or clinical studies: strong (+++); moderate (++); low (+); conflicting data (+/−); not established (–).

[b]High prevalence (≥ 4%; +++); moderate prevalence (1% to < 4%; ++); low prevalence (< 1%; +); not reported (–).

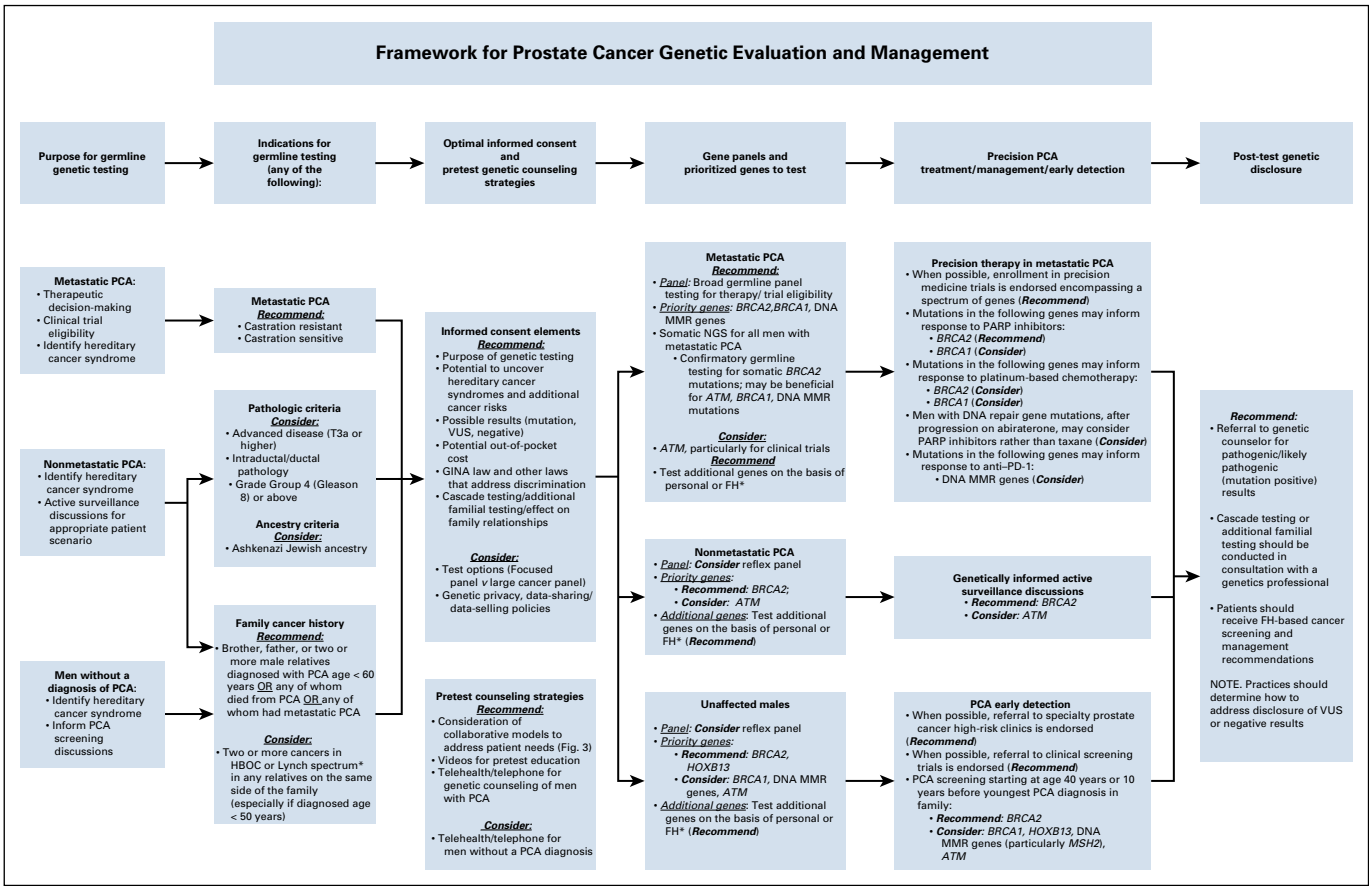


FIG 2. Framework for prostate cancer (PCA) genetic evaluation and management. (*) See Table 2 for personal history or family history (FH) of cancers indicating genes to test. GINA, Genetic Information Nondiscrimination Act; HBOC, hereditary breast and ovarian cancer; MMR, mismatch repair; NGS, next-generation sequencing; PARP, poly (ADP-ribose) polymerase; PD-1, programmed death 1; VUS, variant of uncertain significance.

Panels and genes prioritized for testing:

- **Metastatic PCA**:
  - Comprehensive (large) panel testing for therapy/ clinical trial eligibility (Recommend).
  - **Priority germline testing**:
    - *BRCA2/BRCA1* (Recommend).
    - DNA MMR genes (Recommend).
    - *ATM* (Consider).
    - Test additional genes on the basis of personal or FH (Recommend).
  - **Somatic testing**:
    - Somatic next-generation sequencing for all men with metastatic PCA (Recommend).
    - Confirmatory germline testing for somatic mutations:
      - *BRCA2* (Recommend).
      - *BRCA1,* DNA MMR genes, *ATM* (Consider).
    - Test additional genes on the basis of personal or FH (Table 2; Recommend).
- **Nonmetastatic PCA**:
  - Reflex testing may be optimal (Consider).
  - Priority genes particularly to inform AS:
    - *BRCA2* (Recommend).
    - *ATM* (Consider).
    - Test additional genes on the basis of personal or FH (Table 2; Recommend).
- **Men without a diagnosis of PCA meeting FH testing criteria**:
  - Reflex testing may be optimal (Consider).
  - Priority genes for risk assessment:
    - *BRCA2* (Recommend).
    - *HOXB13* (Recommend).
    - *BRCA1, ATM,* DNA MMR genes (Consider).
    - Test additional genes on the basis of personal or FH (Table 2; Recommend).

Additional considerations. For men with metastatic PCA, broader panel testing may be appropriate, particularly if considering treatment or clinical trial options (Table 2, Fig 2, and Data Supplement). Reflex testing may be considered for all patients, but especially for men with nonmetastatic disease considering AS or men without PCA for early detection, which allows for initial testing of genes that inform management (Data Supplement). Reflex testing also allows for testing of additional genes to account for personal cancer or FH at a later time for comprehensive

genetic evaluation and may also be more amenable to collaborative genetic evaluation models (see below).

Among MMR genes, *MSH2* has the strongest association to PCA; however, it is recognized that *MLH1, PMS2, MSH6,* and *EPCAM* also need to be tested to establish the diagnosis of Lynch syndrome. Full MMR testing also may be important for treatment consideration or clinical trials in the metastatic setting; therefore, full Lynch syndrome testing is recommended as indicated.

In addition, confirmatory GT is recommended for men with somatic *BRCA2* mutations and may be beneficial for somatic mutations in *BRCA1,* MMR genes, and *ATM* to identify hereditary cancer predisposition. Additional GT beyond these genes may also be recommended on the basis of personal and FH. Consultation with a genetics professional is advised.

3. What PCA-Specific Recommendations Should Be Considered on the Basis of Genetic Results?

Gaps addressed. There is a need for consensus agreement on genetically informed PCA treatment, management, and early detection[1,2] (Data Supplement). An additional challenge is inconsistency in NCCN genetically based PCA early detection recommendations regarding which genes to consider and the age at which to begin screening[8,9] (Data Supplement).

Genetically based recommendations. Genes considered included *BRCA1*, *BRCA2*, *HOXB13*, *CHEK2*, *ATM*, *NBN*, *MSH2*, *MSH6*, *MLH1*, *PMS2*, *PALB2*, *BRIP1*, *TP53*, and Fanconi anemia genes.

- **Metastatic PCA**: GT to inform precision therapy:
  - Enrollment of men with PCA in precision medicine trials is endorsed (Recommend).
  - Mutations in the following genes may inform response to PARP inhibitors:
    - *BRCA2* (Recommend).
    - *BRCA1* (Consider).
  - Mutations in the following genes may inform response to platinum-based chemotherapy:
    - *BRCA2* (Consider).
    - *BRCA1* (Consider).
  - Men with DNA repair gene mutations, after progression on abiraterone, may proceed with PARP inhibitor rather than taxane (Consider).
  - Germline mutations in the following genes may inform response to anti–programmed death 1 (PD-1) therapy:
    - DNA MMR genes (Consider).
    - NOTE. The US Food and Drug Administration has granted accelerated approval for anti–PD-1 therapy for microsatellite instability-high/MMR-deficient tumors.
- **Nonmetastatic PCA**: to inform AS discussions:
  - *BRCA2* (Recommend).
  - *ATM* (Consider).
- **Men without a PCA diagnosis to inform PCA early detection**:
  - Referral to specialty PCA high-risk clinics and/or early detection trials was endorsed (Recommend).
  - PCA early detection starting at age 40 years or 10 years before the youngest PCA diagnosis in family:
    - *BRCA2* (Recommend).
    - *BRCA1, HOXB13, ATM,* and DNA MMR genes (particularly *MSH2*; Consider).

Additional considerations. In the metastatic setting, a broad spectrum of genes may be important in determining clinical trial eligibility, and emerging data should continue to refine recommendations. *ATM* garnered consideration for testing, primarily for clinical trial eligibility; however, the panel did not feel that there was sufficient data to endorse *ATM* for informing therapy to PARP inhibitors off study because of the limited independent association to PARP inhibitor response at this time (Data Supplement). *ATM* also garnered moderate consensus for informing AS, but there are limited data at this time (Data Supplement).

For anti–PD-1 therapy, the US Food and Drug Administration has granted accelerated approval for tumors that are microsatellite instability-high or MMR deficient. The panel had moderate consensus regarding a definitive recommendation for anti–PD-1 therapy off study for men with germline MMR mutations, with stronger consideration for clinical trials.

Regarding AS discussions, clinicopathologic criteria, age, and overall health must be considered. *BRCA1* did not achieve consensus for inclusion in AS as a result of limited data for PCA aggressiveness (Data Supplement). Polygenic risk score data were reviewed[77-81] and did not achieve consensus.

4. What Is Optimal Informed Consent for PCA GT?

Gaps addressed. Current practice guidelines do not provide guidance to health care providers regarding optimal informed consent for PCA GT.

Optimal pretest informed consent elements. Ethical considerations of GC were reviewed (Data Supplement). The following elements garnered strong or moderate consensus to discuss with men before GT (Fig 2 and Table 3):

- Recommend discussing: (1) the purpose of GT; (2) the possibility of uncovering hereditary cancer syndromes; (3) potential types of test results; (4) the potential to uncover additional cancer risks; (5) potential out-of-pocket cost; (6) Genetic Information Nondiscrimination Act law and other laws that address genetic discrimination; and (7) cascade testing/additional familial testing.
- Consider discussing: (1) multigene panel options; (2) data sharing/data selling policies of genetic laboratories; and (3) the privacy of genetic tests.

TABLE 3. Priority Elements of Informed Consent for Prostate Cancer Germline Testing

Elements of Informed Consent	Description
Purpose of germline testing	For precision therapy, early detection strategies, and/or to identify hereditary cancer syndrome/risk
Possibility of uncovering hereditary cancer syndromes	Based on FH, testing may include BRCA1 and BRCA2 (associated with hereditary breast and ovarian cancer) or DNA mismatch repair genes (associated with Lynch syndrome; Table 2). Other hereditary syndromes may also be identified.
Panel options	Various multigene panels may be considered for testing (focused PCA panel *v* large cancer panel *v* reflex testing); benefits and risks of each option must be discussed, such as cancer risks uncovered, higher rates of VUS with larger panels, or availability of guidelines for management (Data Supplement).
Potential types of test results	Three main types of results should be discussed, including mutation (pathogenic/likely pathogenic variant), VUS, negative, along with implications of these results on management.
Potential to uncover additional cancer risks	Multiple gene-specific cancer risks may be identified beyond PCA risk that affects men and their families (Table 2).
Potential out-of-pocket cost	Not all insurance plans cover genetic testing for PCA. Some mandate referral to GC. It is important to check with the insurance plan.
Genetic Information Nondiscrimination Act law and other laws that address genetic discrimination	Discuss coverage for health insurance and most employment scenarios. Discuss the lack of coverage for life insurance, long-term care, and disability insurance.
Cascade testing/additional familial testing	Testing blood relatives for pathogenic variants or additional genetic testing on the basis of family history; worry and anxiety that may result from hereditary cancer testing; effect on family relationships
Data-sharing/data-selling policies of genetic laboratories	Each genetic testing laboratory may have unique data-sharing and data-selling policies that patents must be aware of.
Privacy of genetic tests	Protection of genetic data from data breach or access by third parties must be discussed.

Abbreviations: FH, family history; GC, genetic counseling; PCA, prostate cancer; VUS, variant of uncertain significance.

Additional considerations. These elements of pretest informed consent apply to all men who are considering PCA GT[76,82-84] (Fig 2). Such GC aids as handouts or videos may be useful to deliver this information. However, informed consent is a process during which patients have opportunities to ask questions[76,82-84]; therefore, a question-and-answer process must be available before testing. Clinicians without specific training/expertise in GC/GT are urged to refer patients to GC before ordering GT. Furthermore, it is important to remain current on the ethics/informed consent process for GT because of the rapidly evolving nature of precision medicine.

5. What Collaborative Strategies May Facilitate PCA Genetic Evaluation Between Health Care and Genetic Providers?

Gaps addressed. Multidisciplinary guidance on the implementation of collaborative models between health care providers and GC is currently lacking.[103] There is a need to address alternate GC models for timely GT with attention to appropriate pretest informed consent and comprehensive evaluation.

Alternate genetic evaluation delivery strategies. The following strategies were endorsed (Data Supplement and Fig 3):

- Practices should consider multiple models to address patients' needs (Fig 3), including point-of-care models with limited or full pretest FH collection as well as traditional model with upfront referral to GC (Recommend).
- Videos may be useful to deliver pretest informed consent (Recommend).
- In point-of-care models, reflex genetic testing may be optimal to enable additional testing on the basis of personal/FH (Consider).
- Telehealth/telephone delivery of GC is a suitable alternative to in-person GC (Recommend for men with PCA; Consider for unaffected males).

Additional considerations. If limited pretest FH is collected, practices must proactively address the collection of FH in the post-test setting. Reflex testing enables future testing to account for personal/FH. Telehealth/telephone GC was endorsed to address geographic barriers to GC, although patient outcomes data in males are lacking. Key process questions for practices to consider when implementing point-of-care versus traditional GC models were discussed (Data Supplement).

6. What Post-Test Disclosure Strategies Are Most Appropriate Based on Genetic Results?

Gaps addressed. Joint guidance from oncologists, urologists, and genetic counselors for referral to GC is currently lacking.

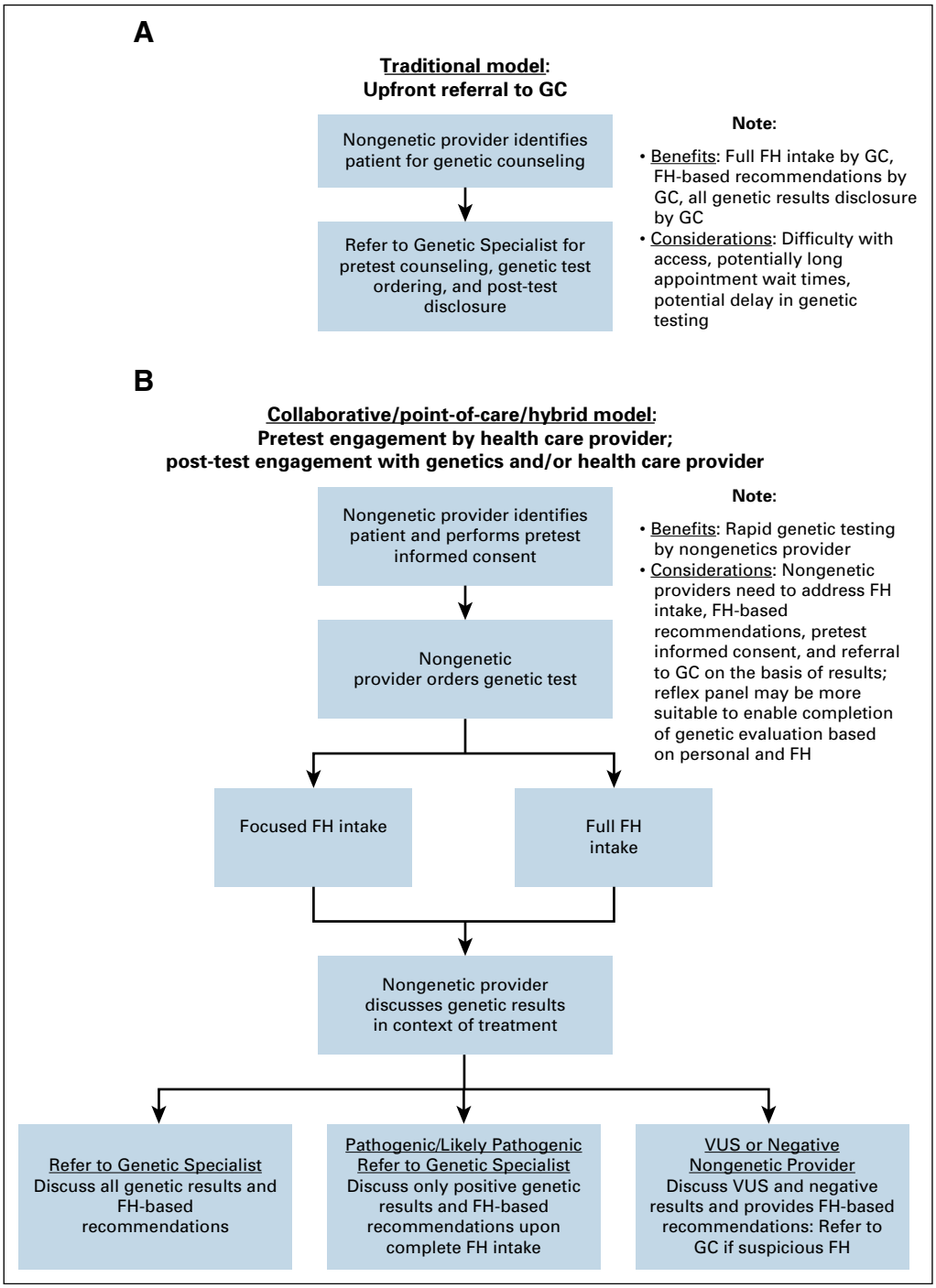


FIG 3. Models of collaboration between genetics and health care practices for prostate cancer genetic evaluation. FH, family history; GC, genetic counseling.

Optimal post-test disclosure strategies:

- Referral to a GC for pathogenic/likely pathogenic results (Recommend).
- Patients should receive FH-based recommendations, either in health care or genetic practices (Recommend).
- Cascade/additional familial testing should be conducted in consultation with a genetic professional (Recommend).

Additional considerations. There was no consensus regarding referral of men with VUS or negative results; therefore, providers will need to determine their ability to discuss VUS results and FH-based recommendations. VUS reclassification to "pathogenic/likely pathogenic" and subsequent management are critical for ordering providers to consider and may support the referral of select men with suspicious VUS to GC. Men with FH of cancers may also warrant referral to GC.

7. What Barriers Must Be Addressed to Enhance PCA GT?

Gaps addressed. Multiple practice, research, and policy gaps pose barriers to PCA GT.

Areas in need of additional attention. The following areas achieved strong or moderate consensus to address:

- Genetic education for providers not formally trained in cancer genetics/genetic counseling (Appendix Table A1, online only, and Data Supplement).
- Barriers to implementation of PCA GT (Appendix Table A2, online only).
- Research priorities (Appendix Table A3, online only).

DISCUSSION

As GT for PCA has rapidly increased, responsible implementation of testing and management are of primary concern.[1,2,19,23] Current practice challenges that pose barriers to operationalizing PCA GT include the variability in testing indications and genetically based management, the need for guidance on panels and priority genes to test, and guidance regarding alternate evaluation models to address GC demand. The 2019 Philadelphia Prostate Cancer Consensus Conference was a focused attempt to address these critical challenges and practice gaps by developing a first-in-field working framework for PCA genetic evaluation, management, and implementation informed by best evidence and expert guidance.

The strength of the consensus framework is the creation of a unified approach regarding GT indications, genetically informed management and treatment, and the integration of GC. Multiple aspects of the framework had strong evidence and strong expert agreement to deem a definitive action of "Recommend". The strongest recommendations encompassed testing all men with metastatic PCA or men with FH suggestive of hereditary PCA. Priority genes for testing included *BRCA2, BRCA1*, and the DNA MMR genes in metastatic disease to inform treatment or clinical trials; *BRCA2* for AS discussions; and *BRCA2* and *HOXB13* for PCA early detection discussions. This was the first formal, multidisciplinary endorsement for broad panel testing among men with metastatic PCA, recognizing that genetic information may enable men to enroll in clinical trials. Consensus emerged regarding strategies for PCA early detection on the basis of genetic status. For male carriers of *BRCA2*, a recommendation was made to begin PSA screening at age 40 years or 10 years before the youngest PCA diagnosis in a family and is modeled after colorectal cancer guidelines.[16]

An important aspect to the genetic evaluation framework was the integration of care processes and GC to account for the increasing need for GC. Strong recommendations were made for optimal pretest informed consent. Recommended strategies to deliver GC included collaborative GC models, videos, and telehealth to facilitate GT through health care practices and to collaborate with GC. Reflex testing garnered moderate consensus and may be considered, particularly when using collaborative counseling models to enable upfront testing by health care providers, followed by testing additional genes using GC for comprehensive genetic evaluation. In the post-test setting, strong recommendations were made to refer all men with pathogenic mutations to GC, to conduct cascade testing of relatives under the care of genetics professionals, and to determine the delivery of FH-based recommendations.

The panel dealt with many uncertainties in recommendations which garnered moderate consensus. Whereas many genes have a lower level of evidence for PCA risk, aggressiveness, or treatment response, several clinically available multigene panels include lower evidence genes. To indicate these nuances in limited data or moderate consensus, many criteria were designated as "Consider" in the framework. Pathologic criteria for testing, such as disease stage, intraductal/ductal histology, or Grade Group ≥ 4, garnered moderate consensus and therefore are included as suggestive criteria for testing.[63,65,66] Ashkenazi Jewish ancestry as a standalone criterion achieved moderate consensus, but may be a stronger consideration for testing for men with higher Gleason score per current NCCN guidelines.[8] Whereas PCA has been linked with HBOC and Lynch syndrome, a working definition of familial features that increase the likelihood of detecting germline mutations is needed. As such, having two or more relatives with cancers in the HBOC or Lynch syndrome spectrum garnered moderate consensus as standalone criteria and may be considered for GT on the basis of patient preference and insurance coverage.

Priority genes to test also presented challenges, particularly regarding *ATM*, DNA MMR genes, and *HOXB13*. Initial data have reported that men with *ATM* mutations experienced clinical response to PARP inhibitors[94]; however, follow-up studies have reported a limited independent effect of *ATM*.[99] Similarly, studies in AS had limited association of *ATM* mutations alone with upgrading of biopsies.[7] Until additional data are available, *ATM* was given a designation of "Consider" for testing, recognizing the potential for clinical trial options for *ATM* carriers. Additional uncertainties were encountered regarding prioritizing MMR genes for GT. Among MMR genes, *MSH2* has the highest reported association to PCA.[41] Although other MMR genes have lower or limited association to PCA, the potential to uncover Lynch syndrome and clinical trial eligibility drove the suggestion to consider full Lynch syndrome testing. *MSH2* status may be more informative for PCA early detection discussions.[41] *HOXB13* has strong association to PCA risk and early-onset disease, though screening outcomes data are limited. Therefore, the consensus panel recommended testing for *HOXB13* and to consider the results in early detection discussions. Overall, *BRCA1, HOXB13*, and MMR genes were designated as "Consider"

for beginning screening at age 40 years or 10 years before the youngest PCA diagnosis in the family because of the currently limited screening data.[9] Data from screening studies, such as IMPACT and the National Cancer Institute (ClinicalTrials.gov identifier: NCT03805919), will be important to reconsider strengthening these recommendations.[10] However, this is the first time that screening strategies based on a larger genetic spectrum have been proposed. Additional research in African American males is vitally needed. Future consideration of circulating tumor and cell-free DNA is also warranted.

In conclusion, the 2019 Consensus Conference created the first multidisciplinary PCA genetic implementation framework tailored to the precision medicine era. The framework, which importantly had input from NCCN panel leaders, provides guidance to a spectrum of providers to facilitate timely and responsible PCA GT for the benefit of men and their families.

AFFILIATIONS

[1]Department of Medical Oncology, Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA
[2]Department of Urology, Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA
[3]Department of Cancer Biology, Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA
[4]Department of Medicine, University of Washington, and Fred Hutchinson Cancer Research Center, Division of Clinical Research, Seattle, WA
[5]Duke University School of Medicine and Duke Cancer Institute, Durham, NC
[6]University of Oklahoma College of Medicine, Norman, OK
[7]Genitourinary Malignancies Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD
[8]National Society of Genetic Counselors, Chicago, IL
[9]Prostate Cancer Foundation, Santa Monica, CA
[10]Yale Cancer Center, New Haven, CT
[11]Department of Radiation Oncology, Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA
[12]Dana-Farber Cancer Institute, Boston, MA
[13]Department of Cancer Biology and Genetics, The Ohio State University Comprehensive Cancer Center, Columbus, Ohio
[14]Department of Laboratory Medicine, University of Washington, Seattle, WA
[15]The University of Texas MD Anderson Cancer Center, Houston, TX
[16]Fox Chase Cancer Center, Philadelphia, PA
[17]Roswell Park Comprehensive Cancer Center, Buffalo, NY
[18]Moores UC San Diego Comprehensive Cancer Center, San Diego, CA
[19]Department of Urology, University of California, San Francisco, San Francisco, CA
[20]James Comprehensive Cancer Center and Department of Internal Medicine, The Ohio State University, Columbus, OH
[21]University of California, San Francisco, Cancer Genetics and Prevention Program, San Francisco, CA
[22]Center for Health Research, Genomic Medicine Institute, Geisinger, Danville, PA
[23]Duke University Medical Center, Durham, NC
[24]North Shore University Health System, Evanston, IL
[25]Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA
[26]Northwestern University, Chicago, IL
[27]Departments of Radiation Oncology, Urology, and Medicine, University of California, San Francisco, San Francisco, CA
[28]Advocate Aurora Health, Milwaukee, WI
[29]University of Pennsylvania, Basser Center for BRCA, Philadelphia, PA
[30]Integra Connect, West Palm Beach, FL
[31]University of Washington, Seattle, WA
[32]American Cancer Society, Atlanta, GA
[33]Urology at Royal Melbourne Hospital, North Melbourne, VIC, Australia
[34]Johns Hopkins Medical Institutions, Baltimore, MD
[35]Tulane University, New Orleans, LA
[36]Brady Urological Institute, Johns Hopkins Medicine, Baltimore, MD
[37]City of Hope Comprehensive Cancer Center, Duarte, CA
[38]Washington University School of Medicine, St Louis, MO
[39]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA
[40]Unit of Urology, Division of Oncology, Urological Research Institute, IRCCS Ospedale San Raffaele, Milan, Italy
[41]The Ohio State University, Columbus, OH
[42]Henry Jackson Foundation for the Advancement of Military Medicine, Center for Prostate Disease Research, Department of Surgery, Uniformed Services University and the Walter Reed National Military Medical Center, Bethesda, MD
[43]University of California, San Diego, La Jolla, CA
[44]Memorial Sloan Kettering Cancer Center, New York, NY
[45]University of Chicago, Chicago, IL
[46]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA
[47]National Cancer Institute, National Institutes of Health, Bethesda, MD
[48]Mayo Clinic, Rochester, MN
[49]Department of Urology and Population Health, New York University and Manhattan Veterans Affairs, New York, NY
[50]Harvard Medical School, Boston, MA
[51]University of Pennsylvania, Philadelphia, PA
[51]Brown University, Providence, RI
[53]University of Michigan, Ann Arbor, MI
[54]Midlantic Urology, Phoenixville, PA
[55]Department of Epidemiology, Harvard TH Chan School of Public Health, Boston MA
[56]University of Utah, Huntsman Cancer Institute, Salt Lake City, UT
[57]Abington-Jefferson Hospital, Abington, PA
[58]Prostate Conditions Education Council, Elizabeth, CO
[59]University of Texas Southwestern Medical Center at Dallas, Dallas, TX
[60]University of Minnesota and Masonic Cancer Center, Madison, WI
[61]Cedars-Sinai Medical Center, Los Angeles, CA
[62]Prostate Cancer International, Virginia Beach, VA
[63]Northwestern Medical Group, Urology Department, Chicago, IL
[64]University of Washington and Fred Hutchinson Cancer Research Center, Seattle, WA

CORRESPONDING AUTHOR

Veda N. Giri, MD, Cancer Risk Assessment and Clinical Cancer Genetics, Department of Medical Oncology, Sidney Kimmel Cancer Center, Thomas Jefferson University, 1025 Walnut St, Suite 1015, Philadelphia, PA 19107; Twitter: @KimmelCancerCtr, @vedangiri, @SKCCDirector, e-mail: veda.giri@jefferson.edu.

SUPPORT

Supported by National Institutes of Health Cancer Center Support Grant 5P30CA056036-19, Foundation Medicine, Myriad, Bayer, Clovis Oncology, BioReference Laboratories, Ferring Pharmaceuticals, Philadelphia Father's Day Run, Invitae, AstraZeneca, Janssen Oncology, Roche, UroSeq, Color, OncLive, Physician Education Resource, and MDx Health.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.20.00046.

AUTHOR CONTRIBUTIONS

Conception and design: Veda N. Giri, Karen E. Knudsen, William K. Kelly, William Dahut, Howard R. Soule, Adam P. Dicker, Amanda E. Toland, Mary B. Daly, Peter R. Carroll, Amie Blanco, Ashley Woodson, Mary-Ellen Taplin, Jacqueline Powers, Richard Wender, Anthony Costello, Anne Calvaresi, Thenappan Chandrasekar, James Eastham, Costas Lallas, Ana Maria Lopez, Mark Mann, Martin M. Miner, Lorelei Mucci, Ronald E. Myers, Brock O'Neil, Peter Pinto, Timothy R. Rebbeck, Charles Ryan, E. Michael D. Scott, Leonard G. Gomella

Administrative support: Leonard G. Gomella

Provision of study materials or patients: Veda N. Giri, Leonard G. Gomella

Collection and assembly of data: Veda N. Giri, William K. Kelly, Heather H. Cheng, Kathleen A. Cooney, Scott Weissman, Adam P. Dicker, Saud AlDubayan, Amanda E. Toland, Colin C. Pritchard, Curtis A. Pettaway, Mary B. Daly, James L. Mohler, Peter R. Carroll, Ashley Woodson, Alanna Rahm, Mary-Ellen Taplin, Thomas J. Polascik, Brian T. Helfand, Colette Hyatt, Alicia K. Morgans, Felix Feng, Raoul Concepcion, Daniel W. Lin, Richard Wender, James Ryan Mark, William B. Isaacs, Jianfeng Xu, Jeffrey Weitzel, Lindsey Byrne, Anne Calvaresi, Thenappan Chandrasekar, Patrick T. Gomella, Nathan Handley, Joseph Izes, R. Jeffrey Karnes, Ana Maria Lopez, S. Bruce Malkowicz, Mark Mann, Patrick Mille, Sarah M. Nielsen, Brock O'Neil, Peter Pinto, Wendy Poage, Timothy R. Rebbeck, Howard Sandler, E. Michael D. Scott, Brittany Szymaniak, Neha Vapiwala, Charnita Zeigler-Johnson, Leonard G. Gomella

Data Analysis and interpretation: Veda N. Giri, William K. Kelly, Heather H. Cheng, Kathleen A. Cooney, Michael S. Cookson, William Dahut, Scott Weissman, Daniel P. Petrylak, Colin C. Pritchard, Curtis A. Pettaway, James L. Mohler, J. Kellogg Parsons, Peter R. Carroll, Robert Pilarski, Ashley Woodson, Alanna Rahm, Mary-Ellen Taplin, Thomas J. Polascik, Brian T. Helfand, Alicia K. Morgans, Felix Feng, Michael Mullane, Richard Wender, Arthur L. Burnett, Oliver Sartor, Jeffrey Weitzel, Gerald L. Andriole, Himisha Beltran, Alberto Briganti, David Y. T. Chen, Robert B. Den, Albert Dobi, E. David Crawford, James Eastham, Scott Eggener, Matthew L. Freedman, Marc Garnick, Mark D. Hurwitz, Joseph Izes, R. Jeffrey Karnes, Lucia Languino, Stacy Loeb, Ana Maria Lopez, Kevin R. Loughlin, Grace Lu-Yao, S. Bruce Malkowicz, Mark Mann, Patrick Mille, Martin M. Miner, Todd Morgan, Jose Moreno, Wayne Pinover, Peter Pinto, Ganesh V. Raj, Matthew Schiewer, William Tester, Edouard J. Trabulsi, Neha Vapiwala, Evan Y. Yu, Leonard G. Gomella

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

The authors are grateful to patients and patient advocates who participated in the Consensus Conference: Buehler J., Hegedus A., Kaye P., Martin S., and Waxman S.P.

REFERENCES

1. Giri VN, Hyatt C, Gomella LG: GT for men with prostate cancer: Navigating an expanding new world of genetic evaluation for precision therapy and precision management. J Clin Oncol 37:1455-1459, 2019
2. Cheng HH, Sokolova AO, Schaeffer EM, et al: Germline and somatic mutations in prostate cancer for the clinician. J Natl Compr Canc Netw 17:515-521, 2019
3. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology: Prostate cancer (version 4.2019). https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf
4. Morgans AK, Szymaniak BM: Genetically-informed treatment for advanced and metastatic prostate cancer. Can J Urol 26:54-56, 2019
5. Pritchard CC, Mateo J, Walsh MF, et al: Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med 375:443-453, 2016
6. Carlo MI, Giri VN, Antonarakis ES, et al: Evolving intersection between inherited cancer genetics and therapeutic clinical trials in prostate cancer: A white paper from the Germline Genetics Working Group of the Prostate Cancer Clinical Trials Consortium. JCO Precis Oncol 10.1200/PO.18.00060
7. Carter HB, Helfand B, Mamawala M, et al: Germline mutations in ATM and BRCA1/2 are associated with grade reclassification in men on active surveillance for prostate cancer. Eur Urol 75:743-749, 2019
8. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology: Genetic/familial high-risk assessment: Breast, ovarian, and pancreatic (version 3.2019). https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf
9. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology: Prostate cancer early detection (version 1.2019). https://www.nccn.org/professionals/physician_gls/pdf/prostate_detection.pdf
10. Page EC, Bancroft EK, Brook MN, et al: Interim results from the IMPACT study: Evidence for prostate-specific antigen screening in BRCA2 mutation carriers. Eur Urol 76:831-842, 2019
11. National Cancer Institute: PDQ cancer information summaries: Genetics. https://www.cancer.gov/publications/pdq/information-summaries/genetics
12. Mersch J, Jackson MA, Park M, et al: Cancers associated with BRCA1 and BRCA2 mutations other than breast and ovarian. Cancer 121:269-275, 2015
13. Ryan S, Jenkins MA, Win AK: Risk of prostate cancer in Lynch syndrome: A systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 23:437-449, 2014
14. National Cancer Institute: Genetics of breast and gynecologic cancers (PDQ) –Health professional version. https://www.cancer.gov/types/breast/hp/breast-ovarian-genetics-pdq
15. National Cancer Institute: Genetics of colorectal cancer (PDQ) –Health professional version. https://www.cancer.gov/types/colorectal/hp/colorectal-genetics-pdq
16. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology: Genetic/familial high-risk assessment: Colorectal (version 2.2019). https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf
17. Hall MJ, Forman AD, Pilarski R, et al: Gene panel testing for inherited cancer risk. J Natl Compr Canc Netw 12:1339-1346, 2014
18. Giri VN, Knudsen KE, Kelly WK, et al: Role of genetic testing for inherited prostate cancer risk: Philadelphia Prostate Cancer Consensus Conference 2017. J Clin Oncol 36:414-424, 2018
19. Abacan M, Alsubaie L, Barlow-Stewart K, et al: The global state of the genetic counseling profession. Eur J Hum Genet 27:183-197, 2019
20. Paller CJ, Antonarakis ES, Beer TM, et al: Germline genetic testing in advanced prostate cancer, practices and barriers: Survey results from the Germline Genetics Working Group of the Prostate Cancer Clinical Trials Consortium. Clin Genitourin Cancer 17:275.e1-282.e1, 2019
21. Giri VN: Genetic education and practice considerations of non-genetic providers. Can J Urol 26:44-45, 2019

22. Goggins M, Overbeek KA, Brand R, et al: Management of patients with increased risk for familial pancreatic cancer: Updated recommendations from the International Cancer of the Pancreas Early detection (CAPS) Consortium. Gut 69:7-17, 2020
23. Gomella LG, Knudsen KE, Giri VN: Introduction to the 2019 Philadelphia Prostate Cancer Consensus Program: Implementation of genetic testing for inherited prostate cancer. Can J Urol 26:1-4, 2019
24. National Cancer Institute: Genetics of prostate cancer (PDQ) –Health professional version. https://www.cancer.gov/types/prostate/hp/prostate-genetics-pdq
25. Breast Cancer Linkage Consortium: Cancer risks in BRCA2 mutation carriers. J Natl Cancer Inst 91:1310-1316, 1999
26. Thompson D, Easton DF; Breast Cancer Linkage Consortium: Cancer incidence in BRCA1 mutation carriers. J Natl Cancer Inst 94:1358-1365, 2002
27. Tryggvadóttir L, Vidarsdóttir L, Thorgeirsson T, et al: Prostate cancer progression and survival in BRCA2 mutation carriers. J Natl Cancer Inst 99:929-935, 2007
28. Nyberg T, Frost D, Barrowdale D, et al: Prostate cancer risks for male BRCA1 and BRCA2 mutation carriers: A prospective cohort study. Eur Urol 77:24-35, 2020
29. Edwards SM, Evans DG, Hope Q, et al: Prostate cancer in BRCA2 germline mutation carriers is associated with poorer prognosis. Br J Cancer 103:918-924, 2010
30. Gallagher DJ, Gaudet MM, Pal P, et al: Germline BRCA mutations denote a clinicopathologic subset of prostate cancer. Clin Cancer Res 16:2115-2121, 2010
31. Thorne H, Willems AJ, Niedermayr E, et al: Decreased prostate cancer-specific survival of men with BRCA2 mutations from multiple breast cancer families. Cancer Prev Res (Phila) 4:1002-1010, 2011
32. Castro E, Goh C, Olmos D, et al: Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. J Clin Oncol 31:1748-1757, 2013
33. Akbari MR, Wallis CJ, Toi A, et al: The impact of a BRCA2 mutation on mortality from screen-detected prostate cancer. Br J Cancer 111:1238-1240, 2014
34. Castro E, Goh C, Leongamornlert D, et al: Effect of BRCA mutations on metastatic relapse and cause-specific survival after radical treatment for localised prostate cancer. Eur Urol 68:186-193, 2015
35. Na R, Zheng SL, Han M, et al: Germline mutations in ATM and BRCA1/2 distinguish risk for lethal and indolent prostate cancer and are associated with early age at death. Eur Urol 71:740-747, 2017
36. Boyle J, Cooney KA: DNA repair genes: Contributions to prostate cancer predisposition and aggressiveness. Can J Urol 26:10-11, 2019
37. Ewing CM, Ray AM, Lange EM, et al: Germline mutations in HOXB13 and prostate-cancer risk. N Engl J Med 366:141-149, 2012
38. Xu J, Lange EM, Lu L, et al: HOXB13 is a susceptibility gene for prostate cancer: Results from the International Consortium for Prostate Cancer Genetics (ICPCG). Hum Genet 132:5-14, 2013
39. Salinas CA, Tsodikov A, Ishak-Howard M, et al: Prostate cancer in young men: An important clinical entity. Nat Rev Urol 11:317-323, 2014
40. Bauer CM, Ray AM, Halstead-Nussloch BA, et al: Hereditary prostate cancer as a feature of Lynch syndrome. Fam Cancer 10:37-42, 2011
41. Dominguez-Valentin M, Sampson JR, Seppälä TT, et al: Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: Findings from the Prospective Lynch Syndrome Database. Genet Med 22:15-25, 2020
42. Angèle S, Falconer A, Edwards SM, et al: ATM polymorphisms as risk factors for prostate cancer development. Br J Cancer 91:783-787, 2004
43. Meyer A, Wilhelm B, Dörk T, et al: ATM missense variant P1054R predisposes to prostate cancer. Radiother Oncol 83:283-288, 2007
44. Schumacher FR, Al Olama AAA, Berndt SI, et al: Association analyses of more than 140,000 men identify 63 new prostate cancer susceptibility loci. Nat Genet 50:928-936, 2018 [Erratum: Nat Genet 51:363, 2019]
45. Cybulski C, Górski B, Debniak T, et al: NBS1 is a prostate cancer susceptibility gene. Cancer Res 64:1215-1219, 2004
46. Leongamornlert DA, Saunders EJ, Wakerell S, et al: Germline DNA repair gene mutations in young-onset prostate cancer cases in the UK: Evidence for a more extensive genetic panel. Eur Urol 76:329-337, 2019
47. Rusak B, Kluźniak W, Wokołorczykv D, et al: Inherited NBN mutations and prostate cancer risk and survival. Cancer Res Treat 51:1180-1187, 2019
48. Wang Y, Dai B, Ye D: CHEK2 mutation and risk of prostate cancer: A systematic review and meta-analysis. Int J Clin Exp Med 8:15708-15715, 2015
49. Conti DV, Wang K, Sheng X, et al: Two novel susceptibility loci for prostate cancer in men of African ancestry. J Natl Cancer Inst 109:djx084, 2017
50. Southey MC, Goldgar DE, Winqvist R, et al: PALB2, CHEK2 and ATM rare variants and cancer risk: Data from COGS. J Med Genet 53:800-811, 2016
51. Pakkanen S, Wahlfors T, Siltanen S, et al: PALB2 variants in hereditary and unselected Finnish prostate cancer cases. J Negat Results Biomed 8:12, 2009
52. Mai PL, Best AF, Peters JA, et al: Risks of first and subsequent cancers among TP53 mutation carriers in the National Cancer Institute Li-Fraumeni syndrome cohort. Cancer 122:3673-3681, 2016
53. Amadou A, Achatz MIW, Hainaut P: Revisiting tumor patterns and penetrance in germline TP53 mutation carriers: Temporal phases of Li-Fraumeni syndrome. Curr Opin Oncol 30:23-29, 2018 [Erratum: Curr Opin Oncol 31:52, 2019]
54. Rana HQ, Gelman R, LaDuca H, et al: Differences in TP53 mutation carrier phenotypes emerge from panel-based testing. J Natl Cancer Inst 110:863-870, 2018
55. Robinson D, Van Allen EM, Wu YM, et al: Integrative clinical genomics of advanced prostate cancer. Cell 162:454, 2015
56. Annala M, Struss WJ, Warner EW, et al: Treatment outcomes and tumor loss of heterozygosity in germline DNA repair-deficient prostate cancer. Eur Urol 72: 34-42, 2017
57. Giri VN, Obeid E, Gross L, et al: Inherited mutations in males undergoing multigene panel testing for prostate cancer: Emerging implications for personalized prostate cancer genetic evaluation. JCO Precis Oncol , 2017
58. Antonarakis ES, Lu C, Luber B, et al: Germline DNA-repair gene mutations and outcomes in men with metastatic castration-resistant prostate cancer receiving first-line abiraterone and enzalutamide. Eur Urol 74:218-225, 2018
59. Mateo J, Cheng HH, Beltran H, et al: Clinical outcome of prostate cancer patients with germline DNA repair mutations: Retrospective analysis from an international study. Eur Urol 73:687-693, 2018
60. Giri VN, Hegarty SE, Hyatt C, et al: Germline genetic testing for inherited prostate cancer in practice: Implications for genetic testing, precision therapy, and cascade testing. Prostate 79:333-339, 2019
61. Nicolosi P, Ledet E, Yang S, et al: Prevalence of germline variants in prostate cancer and implications for current genetic testing guidelines. JAMA Oncol 5: 523-528, 2019
62. Lang SH, Swift SL, White H, et al: A systematic review of the prevalence of DNA damage response gene mutations in prostate cancer. Int J Oncol 55:597-616, 2019
63. Schweizer MT, Antonarakis ES, Bismar TA, et al: Genomic characterization of prostatic ductal adenocarcinoma identifies a high prevalence of DNA repair gene mutations. JCO Precis Oncol , 2019

64. Isaacsson Velho P, Silberstein JL, Markowski MC, et al: Intraductal/ductal histology and lymphovascular invasion are associated with germline DNA-repair gene mutations in prostate cancer. Prostate 78:401-407, 2018
65. Pritchard CC: Molecular insights into the germline for prostate cancer initiation, progression, and aggressiveness. Can J Urol 26:24-26, 2019
66. Cheng HH: Germline contributions to metastatic prostate cancer. Can J Urol 26:19-21, 2019
67. AlDubayan SH: Considerations of multigene test findings among men with prostate cancer: Knowns and unknowns. Can J Urol 26:14-16, 2019
68. Giusti RM, Rutter JL, Duray PH, et al: A twofold increase in BRCA mutation related prostate cancer among Ashkenazi Israelis is not associated with distinctive histopathology. J Med Genet 40:787-792, 2003
69. Kirchhoff T, Kauff ND, Mitra N, et al: BRCA mutations and risk of prostate cancer in Ashkenazi Jews. Clin Cancer Res 10:2918-2921, 2004
70. Agalliu I, Gern R, Leanza S, et al: Associations of high-grade prostate cancer with BRCA1 and BRCA2 founder mutations. Clin Cancer Res 15:1112-1120, 2009
71. Chandrasekar T, Gross L, Gomella LG, et al: Prevalence of suspected hereditary cancer syndromes and germline mutations among a diverse cohort of probands reporting a family history of prostate cancer: Toward informing cascade testing for men. Eur Urol Oncol [epub ahead of print on July 2, 2019]
72. Pettaway CA: African American and Asian males: What do we know about germline predisposition to prostate cancer. Can J Urol 26:27-28, 2019
73. Kwon DH, Borno HT, Cheng HH, et al: Ethnic disparities among men with prostate cancer undergoing GT. Urol Oncol 38:80.e1-80.e7, 2020
74. Momozawa Y, Iwasaki Y, Hirata M, et al: Germline pathogenic variants in 7,636 Japanese patients with prostate cancer and 12,366 controls. J Natl Cancer Inst 2019:djz124, 2019
75. Pilarski R: Current prostate cancer genetic testing capabilities and considerations. Can J Urol 26:38-39, 2019
76. Robson ME, Bradbury AR, Arun B, et al: American Society of Clinical Oncology policy statement update: Genetic and genomic testing for cancer susceptibility. J Clin Oncol 33:3660-3667, 2015
77. Al Olama AA, Kote-Jarai Z, Berndt SI, et al: A meta-analysis of 87,040 individuals identifies 23 new susceptibility loci for prostate cancer. Nat Genet 46: 1103-1109, 2014
78. Benafif S, Kote-Jarai Z, Eeles RA: A review of prostate cancer genome-wide association studies (GWAS). Cancer Epidemiol Biomarkers Prev 27:845-857, 2018
79. Toland AE: Polygenic risk scores for prostate cancer: Testing considerations. Can J Urol 26:17-18, 2019
80. Seibert TM, Fan CC, Wang Y, et al: Polygenic hazard score to guide screening for aggressive prostate cancer: Development and validation in large scale cohorts. BMJ 360:j5757, 2018
81. Fritsche LG, Gruber SB, Wu Z, et al: Association of polygenic risk scores for multiple cancers in a phenome-wide study: Results from the Michigan Genomics Initiative. Am J Hum Genet 102:1048-1061, 2018
82. Riley BD, Culver JO, Skrzynia C, et al: Essential elements of genetic cancer risk assessment, counseling, and testing: Updated recommendations of the National Society of Genetic Counselors. J Genet Couns 21:151-161, 2012
83. Hampel H, Bennett R, Buchanan A, et al: A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: Referral indications for cancer predisposition assessment. Genet Med 17:70-87, 2015
84. Institute of Medicine (US) Committee on Assessing Genetic Risks; Andrews LB, Fullarton JE, et al (eds): Assessing Genetic Risks: Implications for Health and Social Policy. Washington, DC, National Academies Press, 1994
85. Stoll K, Kubendran S, Cohen SA: The past, present and future of service delivery in genetic counseling: Keeping up in the era of precision medicine. Am J Med Genet C Semin Med Genet 178:24-37, 2018
86. Patrick-Miller L, Egleston BL, Daly M, et al: Implementation and outcomes of telephone disclosure of clinical BRCA1/2 test results. Patient Educ Couns 93: 413-419, 2013
87. Schwartz MD, Valdimarsdottir HB, Peshkin BN, et al: Randomized noninferiority trial of telephone versus in-person genetic counseling for hereditary breast and ovarian cancer. J Clin Oncol 32:618-626, 2014
88. Gray J, Brain K, Iredale R, et al: A pilot study of telegenetics. J Telemed Telecare 6:245-247, 2000
89. Hilgart JS, Hayward JA, Coles B, et al: Telegenetics: A systematic review of telemedicine in genetics services. Genet Med 14:765-776, 2012
90. Coelho JJ, Arnold A, Nayler J, et al: An assessment of the efficacy of cancer genetic counselling using real-time videoconferencing technology (telemedicine) compared to face-to-face consultations. Eur J Cancer 41:2257-2261, 2005
91. d'Agincourt-Canning L, McGillivray B, Panabaker K, et al: Evaluation of genetic counseling for hereditary cancer by videoconference in British Columbia. BC Med J 50:554-559, 2008
92. Trepanier AM, Allain DC: Models of service delivery for cancer genetic risk assessment and counseling. J Genet Couns 23:239-253, 2014
93. Buchanan AH, Rahm AK, Williams JL: Alternate service delivery models in cancer genetic counseling: A mini-review. Front Oncol 6:120, 2016
94. Mateo J, Carreira S, Sandhu S, et al: DNA-repair defects and olaparib in metastatic prostate cancer. N Engl J Med 373:1697-1708, 2015
95. Pomerantz MM, Spisák S, Jia L, et al: The association between germline BRCA2 variants and sensitivity to platinum-based chemotherapy among men with metastatic prostate cancer. Cancer 123:3532-3539, 2017
96. Abida W, Bryce AH, Vogelzang NJ, et al: Preliminary results from TRITON2: A phase 2 study of rucaparib in patients (Pts) with metastatic castration-resistant prostate cancer (mCRPC) associated with homologous recombination repair (HRR) gene alterations. Ann Oncol 29:viii271-viii302, 2018 (suppl 8)
97. Castro E, Romero-Laorden N, Del Pozo A, et al: PROREPAIR-B: A prospective cohort study of the impact of germline DNA repair mutations on the outcomes of patients with metastatic castration-resistant prostate cancer. J Clin Oncol 37:490-503, 2019
98. European Society for Medical Oncology: Olaparib outperforms enzalutamide or abiraterone acetate in men with mCRPC and HRR alterations. https://www.esmo.org/oncology-news/olaparib-outperforms-enzalutamide-or-abiraterone-acetate-in-men-with-mcrpc-and-hrr-alterations
99. Marshall CH, Sokolova AO, McNatty AL, et al: Differential response to olaparib treatment among men with metastatic castration-resistant prostate cancer harboring BRCA1 or BRCA2 versus ATM mutations. Eur Urol 76:452-458, 2019
100. Wu Y, Yu H, Zheng SL, et al: A comprehensive evaluation of CHEK2 germline mutations in men with prostate cancer. Prostate 78:607-615, 2018
101. Helfand BT, Xu J: GT for prostate cancer prognosis: Implications for AS. Can J Urol 26:48-49, 2019
102. Polascik TJ, Orabi H: Considerations of GT in prostate cancer early detection. Can J Urol 26:46-47, 2019
103. Hyatt C, Russo J, McDougall C: Genetic counseling perspective of engagement with urology and primary care. Can J Urol 26:52-53, 2019

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Implementation of Germline Testing for Prostate Cancer: Philadelphia Prostate Cancer Consensus Conference 2019

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Veda N. Giri
Stock and Other Ownership Interests: Novopyxis (I)

Karen E. Knudsen
Stock and Other Ownership Interests: Pfizer, Genomic Health
Honoraria: CellCentric, Sanofi
Consulting or Advisory Role: CellCentric, Sanofi, Atrin Pharmaceuticals, Context Therapeutics
Research Funding: Celgene
Travel, Accommodations, Expenses: Sanofi, Genentech

William K. Kelly
Honoraria: Janssen Oncology, Bayer
Consulting or Advisory Role: Merck Sharp & Dohme
Research Funding: Sanofi (Inst), Novartis (Inst), Janssen Oncology (Inst), Bayer (Inst), Exelixis (Inst), Seattle Genetics (Inst), Endocyte (Inst), Amgen (Inst), BioClin Therapeutics (Inst), Sarah Cannon Research Institute (Inst), F Hoffman-La Roche (Inst)
Travel, Accommodations, Expenses: Janssen Oncology, Merck Sharp & Dohme

Heather H. Cheng
Research Funding: Inovio Pharmaceuticals (Inst), Sanofi (Inst), Astellas Medivation (Inst), Janssen Oncology (Inst), Clovis Oncology (Inst), Color Foundation (Inst)

Kathleen A. Cooney
Patents, Royalties, Other Intellectual Property: Patent awarded for discovery of HOXB13 as prostate cancer susceptibility gene (Inst)
Travel, Accommodations, Expenses: Boston Scientific (I)

Michael S. Cookson
Honoraria: Merck, Janssen Biotech, Bayer, Astellas Pharma, Myovant Sciences
Consulting or Advisory Role: Merck, Janssen Biotech, MDxHealth, Bayer, Astellas Pharma, Myovant Sciences, TesoRx Pharma, Genomic Health, Ferring Pharmaceuticals, Precision Biopsy

Scott Weissman
Employment: Genome Medical
Stock and Other Ownership Interests: Genome Medical

Howard R. Soule
Leadership: WindMIL
Consulting or Advisory Role: Compugen, WindMIL
Travel, Accommodations, Expenses: Compugen, Sanofi, WindMIL

Daniel P. Petrylak
Stock and Other Ownership Interests: Bellicum Pharmaceuticals, TYME
Consulting or Advisory Role: Bayer, Exelixis, Pfizer, Roche, Astellas Pharma, AstraZeneca, Eli Lilly, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Clovis Oncology, Incyte, Janssen Oncology, Pharmacyclics, Seattle Genetics, Urogen Pharma, Advanced Accelerator Applications, Ipsen
Research Funding: Progenics (Inst), Sanofi (Inst), Endocyte (Inst), Genentech (Inst), Merck (Inst), Astellas Medivation (Inst), Novartis (Inst), AstraZeneca (Inst), Bayer (Inst), Eli Lilly (Inst), Innocrin Pharma (Inst), MedImmune (Inst), Pfizer (Inst), Roche (Inst), Seattle Genetics (Inst), Clovis Oncology (Inst), Bristol Myers Squibb (Inst), Advanced Accelerator Applications (Inst)
Expert Testimony: Celgene, Sanofi

Adam P. Dicker
Leadership: Department of Defense-Prostate Cancer Research Program, NRG Oncology, American Society for Radiation Oncology
Stock and Other Ownership Interests: Oncohost, Self Care Catalyst
Consulting or Advisory Role: EMD Serono, Janssen Oncology, Self Care Catalyst, Celldex, Johnson & Johnson, Roche, Apex, Cybrexa Therapeutics, Oncohost, Thirdbridge, Accordant
Research Funding: Prostate Cancer Foundation
Patents, Royalties, Other Intellectual Property: Recently filed patent "Doped BEO Compounds for Optically Stimulated Luminescence (OSL) and Thermoluminescence (TL) Radiation Dosimetry"
Expert Testimony: Wilson, Socini
Travel, Accommodations, Expenses: Merck, Ferring Pharmaceuticals, Self Care Catalyst, EMD Serono, Oncohost
Other Relationship: Dreamit Ventures
Uncompensated Relationships: Google

Colin C. Pritchard
Consulting or Advisory Role: Promega

Curtis A. Pettaway
Consulting or Advisory Role: Wolters-Kluwer
Research Funding: Beckmann-Coulter, MDxHealth

James L. Mohler
Patents, Royalties, Other Intellectual Property: Mohler JL, Fiandalo M, Watt D, Sviripa V: Compounds and methods to impair androgen receptor (AR) activation, impair dimerization, and/or impair AR transregulation. US provisional patent application 62/839,676, filed 4/27/2019, by Health Research & University of Kentucky Research Foundation (Inst); Mohler JL, Fiandalo M, Watt D, Sviripa V: Inhibitors of androgen receptor activation and methods of making and using same. US provisional patent application 62/890,292, filed 8/22/2019, by Health Research & University of Kentucky Research Foundation (Inst); Mohler JL, Fiandalo M, Watt D, Sviripa V: Spirocyclic dihydrotestosterone as ligand for proteolysis chimeras for AR degradation, imaging agents, and screening tools for the treatment of prostate cancer. US provisional patent application 62/844,062, filed 5/6/2019, by Health Research & University of Kentucky Research Foundation (revised; Inst)

J. Kellogg Parsons
Stock and Other Ownership Interests: Urigen, Pfizer, Johnson & Johnson, Omega Healthcare Investors
Honoraria: Sophiris Bio
Travel, Accommodations, Expenses: Sophiris Bio
Other Relationship: MDxHealth

Peter R. Carroll
Honoraria: Intuitive Surgical
Consulting or Advisory Role: Nutcracker Therapeutics

Amie Blanco
Employment: Biomarin (I)
Stock and Other Ownership Interests: Biomarin (I)

Ashley Woodson
Employment: Genome Medical
Travel, Accommodations, Expenses: Genome Medical

Mary-Ellen Taplin
Honoraria: Janssen-Ortho, Clovis Oncology, Astellas Pharma, Incyte, UpToDate, Research to Practice, Pfizer, Bayer, Amgen, AstraZeneca, Progenics, Guidepoint Global, Celegen, Merck
Consulting or Advisory Role: Janssen-Ortho, Bayer, Guidepoint Global, Best Doctors, UpToDate, Clovis Oncology, Research to Practice, Myovant Sciences, Incyte, Pfizer, AstraZeneca
Research Funding: Janssen-Ortho (Inst), Medivation (Inst), Bayer (Inst), Pfizer (Inst)
Travel, Accommodations, Expenses: Medivation, Janssen Oncology, Tokai Pharmaceuticals, Astellas Pharma, Incyte, Pfizer, Clovis Oncology, Bayer

Thomas J. Polascik
Honoraria: Endocare

Brian T. Helfand
Speakers' Bureau: Exact Sciences, Ambry Genetics

Colette Hyatt
Employment: GenomeSmart
Stock and Other Ownership Interests: GenomeSmart
Consulting or Advisory Role: GenomeSmart

Alicia K. Morgans
Honoraria: Genentech, Janssen Oncology, Sanofi, AstraZeneca, Astellas Scientific and Medical Affairs, Astellas Colombia, Janssen Oncology, Bayer
Consulting or Advisory Role: Genentech, AstraZeneca, Sanofi, Bayer, Astellas Pharma, Janssen Oncology
Research Funding: Bayer, Seattle Genetics, Astellas Pharma, Genentech, AstraZeneca
Travel, Accommodations, Expenses: Sanofi

Felix Feng
Leadership: PFS Genomics
Stock and Other Ownership Interests: PFS Genomics, Nutcracker Therapeutics, SerImmune
Honoraria: Genentech
Consulting or Advisory Role: Bayer, Blue Earth Diagnostics, Celgene, Medivation, Astellas Pharma, Sanofi, Genzyme, EMD Serono, Janssen Biotech
Research Funding: Zenith Epigenetics
Patents, Royalties, Other Intellectual Property: Develop a molecular signature to predict radiation resistance in breast cancer, and this signature was patented by the University of Michigan; in the process of being licensed to PFS Genomics, a company that the author helped found (Inst)

Jacqueline Powers
Employment: Carevive Systems
Honoraria: CureConnect, Myriad Genetics
Consulting or Advisory Role: Carevive Systems
Travel, Accommodations, Expenses: Hospital of the University of Pennsylvania

Raoul Concepcion
Honoraria: Clovis Oncology, InVitae
Consulting or Advisory Role: IntegraConnect
Speakers' Bureau: Astellas Medivation, Janssen Oncology, Dendreon, Amgen

Daniel W. Lin
Consulting or Advisory Role: Astellas Pharma, Clovis Oncology, Dendreon
Research Funding: Genomic Health (Inst), GenomeDx (Inst), MDxHealth (Inst), Magforce

Anthony Costello
Honoraria: Sandoz

Arthur L. Burnett
Honoraria: Myriad Genetics, Novartis Pharmaceuticals, Futura Medical, Astellas Pharma, Boston Scientific (Inst)
Consulting or Advisory Role: Myriad Genetics, Novartis Pharmaceuticals, Futura Medical, Astellas Pharma
Patents, Royalties, Other Intellectual Property: Patents for the development of devices that may be used in pelvic surgeries, such as penile prosthesis implantation
Uncompensated Relationships: Comphya, Reflexonic

Oliver Sartor
Stock and Other Ownership Interests: Eli Lilly, GlaxoSmithKline, AbbVie, Cardinal Health, United Health Group, Varian Medical Systems, PSMA Therapeutics
Consulting or Advisory Role: Bayer, Johnson & Johnson, Sanofi, AstraZeneca, Dendreon, Endocyte, Constellation Pharmaceuticals, Advanced Accelerator Applications, Pfizer, Bristol Myers Squibb, Bavarian Nordic, EMD Serono, Astellas Pharma, Progenics, Noxo, Blue Earth Diagnostics, Myovant, Myriad Genetics, Novartis, Clovis Oncology, Novartis
Research Funding: Bayer (Inst), Johnson & Johnson (Inst), Sanofi (Inst), Endocyte (Inst), Innocrin Pharma (Inst), Merck (Inst), InVitae (Inst), Constellation Pharmaceuticals (Inst), Advanced Accelerator Applications (Inst), AstraZeneca (Inst), Dendreon (Inst), SOTIO
Expert Testimony: Sanofi
Travel, Accommodations, Expenses: Bayer, Johnson & Johnson, Sanofi, AstraZeneca, Progenics

William B. Isaacs
Honoraria: AstraZeneca
Travel, Accommodations, Expenses: AstraZeneca

Jianfeng Xu
Patents, Royalties, Other Intellectual Property: US9534256 B2: Methods and compositions for correlating genetic markers with risk of aggressive prostate cancer; US9534256 B2: Methods and compositions for correlating genetic markers with risk of aggressive prostate cancer; US9732389 B2: Methods and compositions for correlating genetic markers with prostate cancer risk; informal title: 33 SNPs for PCa risk

Jeffrey Weitzel
Speakers' Bureau: AstraZeneca

Himisha Beltran
Consulting or Advisory Role: Janssen Oncology, Genzyme, GlaxoSmithKline, AbbVie, Astellas Pharma, AstraZeneca, Pfizer
Research Funding: Janssen Oncology (Inst), AbbVie (Inst), Stemcentrx (Inst), Eli Lilly (Inst)
Travel, Accommodations, Expenses: Janssen Oncology

Alberto Briganti
Consulting or Advisory Role: Astellas Pharma, Janssen-Cilag, OPKO Health, MDxHealth, Ferring Pharmaceuticals
Speakers' Bureau: Astellas Pharma
Research Funding: Sandoz-Novartis, Merck Sharp & Dohme

David Y. T. Chen
Stock and Other Ownership Interests: Pfizer, Pfizer (I)

Robert B. Den
Employment: Alpha TAU

Albert Dobi
Patents, Royalties, Other Intellectual Property: Inventor of the ERG monoclonal antibody 9FY, licensed by the Biocare Medical; inventor of a urine biomarker panel, licensed by Exosome Diagnostics

E. David Crawford
Speakers' Bureau: Bayer, Ferring Pharmaceuticals

James Eastham
Stock and Other Ownership Interests: 3D Biopsy

Scott Eggener
Consulting or Advisory Role: Sophiris Bio, Francis Medical, InSightec, Profound Medical
Speakers' Bureau: Janssen Pharmaceuticals
Travel, Accommodations, Expenses: Janssen Biotech, InSightec, Sophiris Bio
Uncompensated Relationships: Steba Biotech

Marc Garnick
Stock and Other Ownership Interests: Immunogen, Exelixis, Dr. Consulta (Sao Paulo Brazil), Myovant
Consulting or Advisory Role: Dr. Consulta (Sao Paulo Brazil), Eli Lilly, Amag, Steba Biotech, Agile Therapeutics, Janssen Oncology, Karyop
Expert Testimony: Fitzpatrick Cella Harper and Scinto, US Department of Justice, Meyers ad Flowers

Nathan Handley
Research Funding: Nektar Therapeutics (Inst)

Mark D. Hurwitz
Honoraria: Pyrexar
Consulting or Advisory Role: Neotherma
Speakers' Bureau: Pyrexar
Patents, Royalties, Other Intellectual Property: Provision patent holder for hyperthermia delivery system

R. Jeffrey Karnes
Patents, Royalties, Other Intellectual Property: GenomeDx
Travel, Accommodations, Expenses: GenomeDx

Lucia Languino
Stock and Other Ownership Interests: Johnson & Johnson

Stacy Loeb
Stock and Other Ownership Interests: Gilead Sciences (I)
Consulting or Advisory Role: Bayer, Lumenis
Travel, Accommodations, Expenses: Sanofi

Grace Lu-Yao
Employment: Sun Pharma Advanced Research Company (I)
Leadership: Sun Pharma Advanced Research Company (I)
Stock and Other Ownership Interests: Merck (I)

Todd Morgan
Consulting or Advisory Role: Myriad Genetics, TerumoBCT
Research Funding: Myriad Genetics (Inst), MDxHealth (Inst), GenomeDx (Inst)

Jose Moreno
Stock and Other Ownership Interests: Illumina, Invitae, ThermoFisher Scientific, Exact Sciences, Guardant Health, Bio-Techne
Research Funding: Janssen Pharmaceuticals, Pfizer, Pillar Biosciences

Lorelei Mucci
Research Funding: Sanofi (Inst), Astellas Pharma (Inst), Bayer (Inst), Janssen Pharmaceuticals (Inst)

Ronald E. Myers
Consulting or Advisory Role: Exact Sciences

Sarah M. Nielsen
Employment: Invitae
Stock and Other Ownership Interests: Invitae
Consulting or Advisory Role: AstraZeneca, Merck, Myriad Genetics
Speakers' Bureau: AstraZeneca
Travel, Accommodations, Expenses: Myriad Genetics, AstraZeneca, Invitae

Peter Pinto
Patents, Royalties, Other Intellectual Property: Royalties from US Patent No. 8948845: "System, methods, and instrumentation for image guided prostate treatment", with inventors/authors Brad Wood and Peter Pinto; the National Institutes of Health (NIH) and Philips (InVivo) have a licensing agreement. NIH does not endorse or recommend any commercial products, processes, or services. The views and personal opinions of authors expressed herein do not necessarily state or reflect those of the US Government, nor any official recommendation or opinion of the NIH or National Cancer Institute.

Wendy Poage
Employment: Servier
Stock and Other Ownership Interests: 3D Biopsy
Honoraria: Janssen Oncology, Myriad Genetics
Travel, Accommodations, Expenses: Pfizer, Dendreon, Janssen Oncology, Myriad Genetics

Ganesh V. Raj
Stock and Other Ownership Interests: EtiraRx,C-Diagnostics
Honoraria: Medivation, Janssen Biotech, Sanofi, Astellas Pharma
Consulting or Advisory Role: Pfizer, Bayer
Speakers' Bureau: Astellas Pharma
Research Funding: Janssen Biotech, Bayer
Patents, Royalties, Other Intellectual Property: Licensing

Timothy R. Rebbeck
Honoraria: AstraZeneca (I)
Consulting or Advisory Role: AstraZeneca (I)

Charles Ryan
Honoraria: Janssen Oncology, Bayer
Consulting or Advisory Role: Bayer, Dendreon, AAA
Research Funding: Clovis Oncology (Inst), Sanofi (Inst), Genzyme (Inst)

Howard Sandler
Stock and Other Ownership Interests: Radiogel
Consulting or Advisory Role: Janssen Pharmaceuticals
Other Relationship: Caribou Publishing

E. Michael D. Scott
Employment: Johnson & Johnson (I), Ex Archa, Calcium USA
Consulting or Advisory Role: Vavotar Life Sciences
Travel, Accommodations, Expenses: Vavotar Life Sciences
Other Relationship: International Myeloma Foundation, Prostate Cancer International

William Tester
Honoraria: DAVA Pharmaceuticals
Consulting or Advisory Role: Janssen Oncology

Edouard J. Trabulsi
Consulting or Advisory Role: GenomeDx
Speakers' Bureau: Johnson & Johnson, Janssen Oncology, Astellas Medivation, Pfizer

Neha Vapiwala
Consulting or Advisory Role: Magellan HealthRx

Evan Y. Yu
Consulting or Advisory Role: Janssen Oncology, Bayer, Merck, AstraZeneca, Amgen, QED, Dendreon, Seattle Genetics, Pharmacyclics, Clovis Oncology, Advanced Accelerator Applications, Sanofi, AbbVie, Myovant Sciences
Research Funding: Dendreon (Inst), Merck (Inst), Seattle Genetics (Inst), Daiichi Sankyo (Inst), Taiho Pharmaceutical (Inst), Pharmacyclics (Inst)

Leonard G. Gomella
Consulting or Advisory Role: Janssen Oncology, Astellas Pharma, Pfizer, Clovis Oncology, Bayer
Patents, Royalties, Other Intellectual Property: Patents held by Thomas Jefferson University

No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Priority Topics for Provider Education

Area of Knowledge	Percent Agreement
Recommend	
Purpose of genetic testing	100
Understanding types of results (mutation, VUS, negative)	92
Genetic Information Nondiscrimination Act and other laws that address discrimination	89
Hereditary cancer syndromes (HBOC, Lynch syndrome, HPC) that may be uncovered	86
Test options (focused prostate cancer panel *v* large cancer panel)	86
Additional cancer risks that may be uncovered	84
Potential out-of-pocket costs for genetic testing for patients	84
Privacy considerations of genetic tests	78
Cascade testing/additional familial testing/effect on family relationships	76
Consider	
Choice of laboratory for testing (pros and cons of test accuracy)	68
Data-sharing/data-selling policies of laboratories	62

NOTE. The Data Supplement provides educational resources for providers or trainees regarding germline testing.
Abbreviations: HBOC, hereditary breast and ovarian cancer; HPC, hereditary prostate cancer; VUS, variant of uncertain significance.

TABLE A2. PCA Genetic Testing Implementation Barriers

Barrier	Percent Agreement
Recommend	
Increase advocacy and public awareness for PCA genetic testing and impact of genetic results for men and their families	99
Reimburse telehealth and telephone counseling	98
Implement virtual tumor boards, virtual molecular boards, or virtual genetics boards to disseminate genetics and molecular expertise	79
Redefine “actionability” to include familial impact of genetic testing for payer coverage	75
Consider	
Increase lobbying efforts to enhance payer coverage of PCA genetic testing	64
Engage primary care providers in genetic evaluation for PCA	63

Abbreviation: PCA, prostate cancer.

TABLE A3. Research Priorities to Advance PCA Genetics Knowledge and Practice

Priority Area	Percent Agreement
Recommend	
Genetics of PCA in diverse populations of men	93
Clinical outcomes by germline mutation status	93
Precision medicine trials	88
Precision PCA early detection trials	80
Basic science research into metastatic disease biology	76
Consider	
Implementation outcomes research regarding the alternate delivery of genetic counseling	72
Psychosocial outcomes of men undergoing genetic testing through various clinical approaches	63

Abbreviation: PCA, prostate cancer.

care delivery reviews

Practical Considerations and Challenges for Germline Genetic Testing in Patients With Prostate Cancer: Recommendations From the Germline Genetics Working Group of the PCCTC

Brittany M. Szymaniak, PhD[1]; Lauren A. Facchini, MS[2]; Veda N. Giri, MD[3]; Emmanuel S. Antonarakis, MD[4]; Tomasz M. Beer, MD[5]; Maria I. Carlo, MD[6]; Daniel C. Danila, MD[6]; Mallika Dhawan, MD[7]; Daniel George, MD[8]; Julie N. Graff, MD[9]; Shilpa Gupta, MD[10]; Elisabeth Heath, MD[11]; Celestia S. Higano, MD[12]; Glenn Liu, MD[13]; Ana M. Molina, MD[14]; Channing J. Paller, MD[4]; Akash Patnaik, MD, PhD, MMSc[15]; Daniel P. Petrylak, MD[16]; Zachery Reichert, MD, PhD[17]; Matthew B. Rettig, MD[18]; Charles J. Ryan, MD[10]; Mary-Ellen Taplin, MD[19]; Jake Vinson, BSc[20]; Young E. Whang, MD, PhD[21]; Alicia K. Morgans, MD, MPH[22]; Heather H. Cheng, MD, PhD[12]; and Rana R. McKay, MD[23]

abstract

Germline genetic testing is now routinely recommended for patients with prostate cancer (PCa) because of expanded guidelines and options for targeted treatments. However, integrating genetic testing into oncology and urology clinical workflows remains a challenge because of the increased number of patients with PCa requiring testing and the limited access to genetics providers. This suggests a critical unmet need for genetic services outside of historical models. This review addresses current guidelines, considerations, and challenges for PCa genetic testing and offers a practical guide for genetic counseling and testing delivery, with solutions to help address potential barriers and challenges for both providers and patients. As genetic and genomic testing become integral to PCa care, developing standardized systems for implementation in the clinic is essential for delivering precision oncology to patients with PCa and realizing the full scope and impact of genetic testing.

JCO Oncol Pract 16.

INTRODUCTION

Genomics is rapidly pushing oncology closer to an actualized version of precision medicine.[1,2] In the era of poly (ADP-ribose) polymerase inhibition and immunotherapy, genetic testing may yield information that will affect therapeutic choices, in addition to informing the patient about personal and familial risk.[3-5] Multiple guidelines now include germline genetic testing for men with prostate cancer (PCa), although incorporating testing into clinical workflows remains a challenge.[5,6] This article addresses (1) current guidelines for germline testing, (2) key aspects of testing and counseling, (3) a road map for genetic testing and counseling delivery, (4) challenges of testing and possible solutions, and (5) benefits and limitations of testing.

Germline Genetic Counseling for Men With PCa

Since the landmark article by Pritchard et al[7] that described a relatively high prevalence of germline mutations in DNA repair genes in men with metastatic PCa, other groups have reported the prevalence of germline mutations in PCa ranging between 7.5% and 19%, with *BRCA2* being the highest overall contributor.[8-11] Consequently, several groups issued recommendations for germline testing (Table 1), which place significant demands on clinical workflows and resources for genetic counseling. Genetic counselors (GCs) are trained to assess family histories for genetic risk, provide pretest and post-test counseling, order appropriate testing, and interpret test results. Unfortunately, access to genetic providers is limited, with the majority of the small workforce usually centered in urban areas and academic institutions.[12,13] In 2016, the Genetic Counselor Workforce Working Group estimated a growth of 72% in the workforce between 2017 and 2026, with demand not expected to meet population equilibrium until 2024-2030.[14] This limited access may necessitate other health care providers, including oncologists, urologists, and primary care physicians, to absorb some responsibility for genetic testing. However, these providers may be insufficiently trained in genetics, resulting in inappropriate testing and misinformation.[15-17]

The increased number of men with PCa to be tested and the scarcity of GCs suggest a critical unmet need for expanded genetic services through novel approaches outside of historic delivery models.[18] Evolving service models that incorporate phone and video telemedicine can be particularly useful when geography or public health crises, such as COVID-19, make in-person visits challenging.[19,20] Hybrid service models

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on July 29, 2020 and published at ascopubs.org/journal/op on September 28, 2020: DOI https://doi.org/10.1200/OP.20.00431

that divide responsibilities between physicians and GCs are also options.[21] Collaboration between GCs and clinicians is critical to determine which approach best suits a practice, because there is no one-size-fits-all solution.

Delivery of Germline Testing and Counseling

Initiating genetic testing. One of the greatest hurdles is ensuring that appropriate patients are systematically identified for testing. Developing a plan to consistently screen and identify patients based on current guidelines is necessary (Table 1). Assigning screening to a team member or using patient-completed family history questionnaires can facilitate referral and testing processes. Automated electronic medical record (EMR) features can trigger genetic counseling referrals or alert the clinical team based on a diagnosis code for metastatic PCa or family history/pedigree functionality.

After patients are identified, several options for counseling and testing are available:

1. Referral to a geneticist or GC for in-person, telephone-based, or telemedicine counseling services in response to manual referral or automated EMR triggers.
2. Treating clinicians perform pretest consent and order germline genetic testing directly: If genetic counseling services are unavailable, testing is urgent, or workflow supports providers initiating testing, treating providers can perform pretest education, obtain informed consent, and order genetic testing.[21] Providers should consider any clinical, psychosocial, and financial issues when determining whether to pursue testing within their practice or refer to a remote/telehealth genetic service if they do not have access within the practice.
3. Patient-initiated testing (PIT) platforms: Some commercial genetic testing laboratories, such as Color and Invitae, offer clinical-grade testing that can be initiated by the patient. This process may involve a pretest clinician review and the option for post-test genetic counseling. However, there remain concerns about guidance on test selection, limitations in genetic counseling, lack of follow-up regarding future reclassification of variants, potential for misinterpretation of results, and propagation of misinformation within families. Furthermore, PIT may not include genes important to a patient's personal or family history, potentially creating a false sense of reassurance if testing is negative. Given this, provider-initiated testing is preferred.
4. Direct-to-consumer (DTC) testing platforms: DTC genetic testing has become increasingly popular, likely because of easy access and no medical provider oversight. DTC testing is not comprehensive and should not be considered a substitute for clinical-grade testing. Although 23&Me has Food and Drug Administration approval to report on the three known Ashkenazi Jewish BRCA1/2 founder variants, the National Comprehensive Cancer Network (NCCN) cautions that any results should be confirmed with a clinical-grade test.[22] Providers should be skeptical of any raw data findings from secondary companies, such as Promethease, which are prone to false positives and false negatives.[23]

Family cancer history intake. Although all patients with high-risk localized or metastatic PCa should undergo germline genetic testing regardless of family history, accurately evaluating a patient's personal and family history is essential to determine whether patients need a broader germline panel. Furthermore, gathering a family history can help inform personal and family screening recommendations in the event of negative testing. Cancer counseling sessions include a three- to four-generation pedigree with information on maternal and paternal relatives with cancer, age of diagnosis, age/cause of death, and any prior genetic testing.[22,24] For relatives with PCa, the Gleason grade, metastatic status, and/or cause of death can be useful. Information about ancestry (eg, Ashkenazi Jewish) and consanguinity should be noted. Family history questionnaires can be completed in the clinic or electronically.

Complete family histories ensure that the most informative, cost-effective testing is performed. Although the presence of other cancer types in a family history may be explained by a mutation in a PCa predisposition gene, providers should consider expanded testing for genes related to the observed cancers in a family history when necessary. For instance, hereditary pancreatic cancer and PCa typically occur in the setting of a pathogenic *BRCA2* variant. However, it may be reasonable to include other genes associated with pancreatic cancer, such as *CDKN2A* and *CDK4*.

Somatic next-generation sequencing. Somatic next-generation sequencing tumor testing is increasingly used to guide treatment decision making and can be performed in parallel with germline testing. In addition to detecting tumor-specific mutations, it can sometimes identify potential germline mutations. Most somatic testing platforms are not validated to distinguish germline from somatic-only mutations, even if paired testing with a blood or saliva sample is performed. Thus, a referral to genetics is recommended to determine whether confirmatory or more comprehensive testing is warranted. Providers should consider the variant allele frequency, actionability of the gene, classification of the variant, and tumor type when reviewing somatic variants for possible germline origin.[25]

Pretest education and informed consent. Pretest education and informed consent discussions should review the purpose of testing; general information about included genes; possible test results (Table 2); medical management implications; review of possible benefits, risks, and limitations (Table 3); and the voluntary nature of testing.[24,26] Several major medical societies have also published detailed guidelines reviewing the components of pretest counseling and informed consent to help clinicians.[24] Clinical teams

TABLE 1. Summary of the Current PCa Genetic Testing Guidelines

Organization	Source	Guidelines	Genes
National Comprehensive Cancer Network	Genetic/familial high-risk assessment: breast, ovarian, and pancreatic version 1.2020[22]	Testing is clinically indicated in the follow scenarios:	*ATM* *BARD1*[a] *BRCA1* *BRCA2* *BRIP1* *CDH1*[a] *CDKN2A*[a] *CHEK2* *MSH2* *MLH1* *MSH6* *PMS2* *EPCAM* *NBN* *NF1*[a] *PALB2* *PTEN*[a] *RAD51C* *RAD51D* *STK11*[a] *TP53*
	Hereditary cancer testing criteria	1. Individuals with any blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene	
		2. Individuals meet the criteria below but with previous limited testing (eg, single gene and/or absent deletion duplication analysis) interested in pursuing multigene testing	
		3. Personal history of cancer	
		• Metastatic or intraductal PCa at any age	
		• High-grade (Gleason score ≥ 7) PCa with:	
		o Ashkenazi Jewish ancestry; or	
		o ≥ 1 close relative with breast cancer at age ≤ 50 years or ovarian, pancreatic, or metastatic or intraductal PCa at any age; or	
		o ≥ 2 close relatives with breast or PCa (any grade) at any age	
		• A mutation identified on tumor genomic testing that has clinical implications if also identified in the germline	
		• To aid in systemic therapy decision making	
		4. Family history of cancer	
		• An affected or unaffected individual with a first- or second-degree blood relative meeting any of the criteria listed above (except individuals who meet criteria only for systemic therapy decision making)	
		There is a low probability (< 2.5%) that testing will have findings of documented clinical utility in the following scenarios:	
		• Men diagnosed with localized PCa with Gleason score < 7 and no close relative with breast, ovarian, pancreatic, or PCa	
National Comprehensive Cancer Network	Prostate cancer, version 1.2020[44]	Germline testing is recommended for patients with PCa and any of the following:	*ATM* *BRCA1* *BRCA2* *CHEK2* *HOXB13* *MLH1* *MSH2* *MSH6* *PALB2* *PMS2*
		• High-risk, very-high-risk, regional, or metastatic PCa	
		• Ashkenazi Jewish ancestry	
		• Family history of high-risk germline mutations (eg, *BRCA1/2*, Lynch mutation)	
		• A positive family history of cancer:	
		o A strong family history of PCa consists of: brother or father or multiple family members who were diagnosed with PCa (but not clinically localized Grade Group 1) at < 60 years of age or who died from PCa; OR	
		o ≥ 3 cancers on same side of family, especially diagnoses ≤ 50 years of age: bile duct, breast, colorectal, endometrial, gastric, kidney, melanoma, ovarian, pancreatic, prostate (but not clinically localized Grade Group 1), small bowel, or urothelial cancer	

(continued on following page)

TABLE 1. Summary of the Current PCa Genetic Testing Guidelines (continued)

Organization	Source	Guidelines	Genes
Expert Panel	Philadelphia Consensus meeting publication, 2017[45]	Men meeting any one of the following suggested criteria should undergo genetic counseling and genetic testing: • All men with PCa from families meeting established testing or syndromic criteria for the following: o HBOC (Consensus: 93%) o HPC (Consensus: 95%) o LS (Consensus: 88%) • Men with PCa with two or more close blood relatives on the same side of the family with a cancer in the following syndromes: o Post-consensus discussion included consideration of age cutoff for this criterion. A specific age cutoff will require additional data, and age at diagnosis is important to inquire about in the genetic counseling session with patients. ■ HBOC (Consensus: 93%) ■ HPC (Consensus: 86%) ■ LS (Consensus: 86%) • All men with metastatic castrate-resistant PCa should consider genetic testing (Consensus: 67%). Post-consensus discussion also included consideration of testing men with metastatic, hormone-sensitive PCa to identify germline mutations to inform potential future treatment options and cascade testing in families. Men with tumor sequencing showing mutations in cancer-risk genes should be recommended for germline testing, particularly after factoring in additional personal and family history (Consensus: 77%).	*ATM* *BRCA1* *BRCA2* *HOXB13* *MSH2* *MLH1* *PMS2* *MSH6*
AUA	Clinically localized PCa: AUA/ASTRO/SUO guideline, 2017[46]	The Panel recommends that clinicians take a detailed family history of cancers and give consideration to patient referral for genetic screening and counseling for men with localized high-risk PCa, particularly in the setting of family history of first-degree relatives with cancers of breast, ovary, pancreas, other GI cancers, and lymphoma.	No genes specified for germline testing

Abbreviations: ASTRO, American Society of Therapeutic Radiation and Oncology; AUA, American Urological Association; HBOC, hereditary breast and ovarian cancer syndrome; HPC, hereditary prostate cancer; LS, Lynch syndrome; PCa, prostate cancer; SUO, Society of Urologic Oncology.

[a]These genes are not currently associated with PCa.

should note the requirements for documentation of informed consent, which differ by state and institutional policies.

Test selection and ordering. Many commercial laboratories offer clinical genetic testing for hereditary cancer syndromes. Testing panels range from targeted, guidelines-based panels to comprehensive, pan-cancer panels that may include preliminary evidence genes. Some major laboratories, such as Ambry Genetics, Invitae, and GeneDx, offer PCa-specific panels that include the following genes: *ATM, BRCA1, BRCA2, CHEK2, HOXB13, MLH1, MSH2, MSH6, NBN, PALB2, PMS2,* and *TP53*. Genetic testing panels are subject to change, and decisions regarding specific genetic tests should be individualized based on factors such as laboratory reputation and quality, insurance networks, genes offered and customizability of panels, laboratory billing practices, follow-up testing options for family members, turnaround times, and availability of genetic counseling services.

Clinicians should recognize that larger panels increase the probability of detecting variants of uncertain significance (VUS), incidental/secondary findings (pathogenic variants in genes not related to hereditary PCa), and variants associated with syndromes that may be outside of the scope of clinicians treating PCa (Tables 2 and 3). Clinical workflows must ensure that tasks involved with ordering genetic testing include determination of insurance coverage and submission of orders, standardized collection and shipment of samples, and a clear chain of responsibility.

Insurance coverage for germline testing is in flux. Although the cost of genetic testing has decreased, the possible out-of-pocket (OOP) cost for patients can be difficult to discern because of the varying billing policies of laboratories and insurance coverages.[27] Although the NCCN hereditary breast and ovarian cancer guidelines (v3.2019) are often the primary source used by payers, including Medicare, to develop coverage policies, most have their own criteria that

TABLE 2. Possible Genetic Test Results[47,48]

Interpretation	Result	Definition
Positive	Pathogenic	An alteration in the DNA that is associated with increased disease risk.
	Likely pathogenic	An alteration in the DNA that is likely to be associated with increased disease risk. Meets most but not all criteria to be classified as pathogenic.
Uncertain	Variant of uncertain significance	An alteration in the DNA that may or may not be disease causing. Insufficient evidence to classify as either pathogenic or benign.
Negative	Likely benign	An alteration in the DNA that is unlikely to be associated with increased disease risk. Meets most but not all criteria to be classified as benign.
	Benign	An alteration in the DNA that is not associated with increased disease risk.

determine testing coverage. These criteria may not be up to date with current NCCN guidelines, potentially excluding PCa from their criteria completely, and may mandate a consultation with certified GC for approval.

Many, but not all, laboratories work with commercial insurance companies to negotiate coverage into their policies and will provide an estimate of the OOP cost of testing. Not all insurance companies require prior authorization for genetic testing. Laboratory online ordering portals will often indicate whether provider-initiated insurance prior authorization is needed. Typically, all components of the billing process, including submission of insurance prior authorization, are handled by the laboratory. Several commercial laboratories offer a patient-pay or fixed OOP cost, often $250 or lower, making testing more financially accessible. In addition, patients may qualify for a sponsored testing program at no cost in exchange for de-identified data shared with the sponsoring companies.

Results delivery and follow-up. Methods for delivering test results vary, depending on workflow, availability of genetic counseling services, and provider comfort level and training. Regardless of result type, genetic test reports should be offered to patients for their own records and uploaded into the EMR. Refer to Table 2 for information regarding the following result types. Options for returning results include:

1. Ordering provider refers all patients for post-test counseling, either through referral to a local GC or a telehealth genetic counseling service.
2. Ordering provider refers patients with complex results (eg, positive and/or VUS) for post-test counseling. This type of blended approach to genetic testing has been previously discussed and has received strong consensus across multiple disciplines.[21,26]
   a) Negative results: Clinical teams can disclose results via telephone, patient portal message, a follow-up appointment, or a letter summarizing the results and providing contact information if there are questions. A templated letter can be generated with GC input. Cancer screening recommendations should be based on the family history and should be reviewed with the patient. For example, men with a first-degree relative with PCa remain at increased risk for PCa and should initiate prostate screening at a younger age per routine guidelines. Patients should be encouraged to discuss updates to personal and family history, which may prompt consideration of additional genetic testing or altered screening recommendations.
3. Ordering provider discloses all result types. It is important to note that even in this situation, a referral can be made to genetics for post-test counseling.
   a) Positive results: Providers should discuss and document the implications of the results in terms of cancer risks associated with the identified gene mutation, additional cancer screening recommendations, appropriate referrals, and possible implications for treatment. Providers should also recommend cascade testing, which entails genetic

TABLE 3. Pretest Talking Points Regarding the Benefits and Risks/Limitations of Genetic Testing[27,49]

Benefits	Risks/Limitations
May help explain personal cancer history	May increase anxiety and guilt regarding hereditary cancer risk
May help inform prognosis	Potential for uncertain results: 1) Variants of uncertain significance, or 2) Positive results in lesser established genes and those with no management guidelines currently available
May help inform risks for additional cancers	Genetic discrimination risks (life insurance or long-term care insurance)
May help guide treatment decisions	Financial barriers
May help inform cancer risks for family members	

counseling and testing in at-risk relatives of individuals identified to carry specific genetic mutations or further testing in the family based on family history. Access to the proband's test report will be essential for family members considering testing.

b) VUS results: It is critical to review the uncertainty of whether the specific gene mutation identified is disease causing or a benign variation. The vast majority of VUS results are later reclassified to negative[28,29]; thus, they are typically treated as negatives, and screening recommendations are made based on personal and family history. Testing family members for a VUS is typically not recommended unless it is in the context of a variant resolution or research program. When a VUS is reclassified, new reports are customarily issued to the ordering provider, and it is therefore the responsibility of the ordering provider to follow up with patients over the long term concerning any reclassifications. Patients should be encouraged to check in with their providers every few years to see whether there are updates to the classification. It is also important to note the possibility of discrepant variant classifications across laboratories. These discrepancies may cause difficulty determining how to appropriately manage patients and family members. ClinVar is a free, publicly available database that aggregates variant classifications, although a limitation is that entry submissions may not be completely up to date.

Cascade testing. The concept of cascade testing should be introduced as part of pretest counseling. Family letters can facilitate genetic testing for other relatives in the event of a positive result and typically include a short description of the cancer syndrome, the specific mutation identified, information on how to contact a GC in their area, and laboratory/specimen identification for the patient's testing. A number of the genes associated with hereditary PCa, such as *BRCA1/2* and the mismatch repair genes, are associated with additional cancers and may have well-defined risk numbers and screening recommendations for males and females. Targeted testing for the known familial variant can clarify the cancer risks for other relatives, allowing for the initiation of appropriate increased cancer screening and risk-reducing therapies, and consideration of reproductive planning options.[27] Ultimately, it is the patient's decision and responsibility to inform at-risk relatives about their genetic test results, which underlies the importance of reviewing cascade testing and providing resources to help facilitate this transfer of critical information.

Additional Considerations

Pathogenic mutations identified in DNA-damage repair genes, such as *BRCA1/2* or mismatch repair genes, have implications for management and treatment.[3,4] Germline mutations are identified in approximately 12% of patients with metastatic PCa, but because some are not actionable, it is important to manage expectations concerning outcomes for germline testing.[7-11] Many of the genes included on PCa panels are newly associated with PCa and do not yet have well-defined cancer risks. This increases the possibility of a positive result in a gene associated with low-to-moderate increased cancer risk, which may not have clear screening recommendations. Providers need to be clear about the preliminary nature of findings and that there may not be an immediate impact on cancer screening or treatment options. Patients and their families should be encouraged to participate in registries or research studies to better characterize the risk associated with specific variants over time. Providers can refer patients to a GC for further discussion. Finally, as germline mutations continue to be levied for treatment purposes, providers must be aware of the risk of secondary malignancies and treatment-related adverse effects in some mutation carriers.[28-32]

Some providers may be concerned about the potential for negative consequences from genetic testing. A number of studies have found that most individuals are unlikely to experience significant psychological distress after receiving genetic test results.[33,34] Notably, the likelihood of psychological distress, family disruption, and nonadherence to surveillance guidelines was greater in settings without adequate patient education, counseling, informed consent, and follow-up.[33,35] A recent study of men with PCa undergoing genetic testing found genetic counseling to be beneficial.[35]

Some patients are hesitant about genetic testing because of concerns about discrimination. The Genetic Information Nondiscrimination Act (GINA), a federal law passed in 2008, protects individuals from genetic discrimination from health insurance companies and employers, with specific limitations on the type of employer and size of the company. Importantly, GINA protections do not extend to life, disability, or long-term care insurance. Some states have passed genetic discrimination laws that extend protection beyond GINA. Information regarding GINA is often included in the consent forms for testing laboratories, and summary handouts could be given to patients with additional questions.

Practical Strategies to Overcome Genetic Service Barriers

ASCO and other major health societies strongly encourage and often provide additional education training for non-genetics providers who are interested in responsibly incorporating genetic services into their practice. Courses on genomic cancer risk assessment for physicians, advanced practice providers, nurses, GCs, and other health care professionals are available through organizations such as City of Hope, American Urological Association, and ASCO.

Alternatives to in-person pretest counseling, such as educational handouts, videos, and presentations, are allowing genetic counseling expertise to be shifted to the post-test setting, prioritizing visits for complex counseling patients and/or abnormal results, and facilitating a hybrid service

delivery model.[18,36] Data are still emerging regarding the effectiveness of these models and patient satisfaction. Other practical strategies have focused on increasing GC efficiency and patient volumes, leading to the creation of new support roles, such as GC assistants; incorporation of technologies that reduce appointment time, such as online pedigree collection tools; and group genetic counseling sessions.[37,38] There are now chatbots, such as Genetic Information Assistance, that can converse with patients about family history and the basics of genetic testing and insurance, and determine who qualifies for genetic testing.

Special attention and strategies to minimize disparities in genetics are essential. It has been well documented that socioeconomically disadvantaged individuals, racial/ethnic minorities, and men are less likely to receive genetic services.[18,39-43] PCa genetic testing provides a unique opportunity for providers and institutions to address possible disparities and consider offering counseling services within a male-friendly environment. It is imperative that health care providers from all specialties work together to provide equal access to genetic services by minimizing biases, improving patient education and understanding, creating culturally sensitive interfacing materials, and expanding services to underprivileged areas.

In conclusion, as genetic testing becomes integral to the care of patients with PCa, coordinated efforts across multiple disciplines are required to deliver optimal care. Developing creative, scalable strategies to deliver high-quality personalized genetics care for patients with PCa will be paramount to realizing the full scope and impact of genetic testing for individual patients and family members. It is clear that expanding education around the need for testing and developing standardized systems for implementation in the clinic are important directions for genetics care delivery and essential for delivering precision oncology to men with PCa.

AFFILIATIONS

[1]Department of Urology, Feinberg School of Medicine at Northwestern University, Chicago, IL
[2]Seattle Cancer Care Alliance, Seattle, WA
[3]Thomas Jefferson University, Philadelphia, PA
[4]Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD
[5]Knight Cancer Institute, Oregon Health & Science University, Portland, OR
[6]Sidney Kimmel Center for Prostate and Urologic Cancers, Memorial Sloan Kettering Cancer Center, New York, NY
[7]Division of Hematology/Oncology, University of California San Francisco, CA
[8]Division of Medical Oncology, Department of Medicine, and Duke Cancer Institute, Duke University Medical Center, Durham, NC
[9]Division of Hematology and Medical Oncology, VA Portland Health Care System/Oregon Health & Science University Knight Cancer Institute, Portland, OR
[10]Division of Hematology, Oncology, and Transplantation, University of Minnesota Masonic Cancer Center, Minneapolis, MN
[11]Karmanos Cancer Institute and Department of Oncology, Wayne State University, Detroit, MI
[12]Fred Hutchinson Cancer Research Center and Division of Medical Oncology, Department of Medicine, University of Washington School of Medicine, Seattle, WA
[13]University of Wisconsin, Madison, WI
[14]Division of Hematology and Medical Oncology, Department of Medicine, Weill Cornell Medical College, New York, NY
[15]Department of Medicine, University of Chicago Comprehensive Cancer Center, Chicago, IL
[16]Department of Urology, Yale Cancer Center, New Haven, CT
[17]Department of Internal Medicine, Division of Hematology/Oncology, University of Michigan, Ann Arbor, MI; University of Michigan Rogel Cancer Center, Ann Arbor, MI
[18]Division of Hematology-Oncology, Department of Medicine, David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA
[19]Department of Medical Oncology, Dana Farber Cancer Institute, Boston, MA
[20]The Prostate Cancer Clinical Trials Consortium, New York, NY
[21]Department of Medicine, Hematology/Oncology, University of North Carolina Lineberger Cancer Center, Chapel Hill, NC
[22]Division of Hematology/Oncology, Department of Medicine, Feinberg School of Medicine at Northwestern University, Chicago, IL
[23]Department of Medicine, University of California at San Diego Moores Cancer Center, La Jolla, CA

CORRESPONDING AUTHOR

Rana R. McKay, MD, Moores Cancer Center, University of California San Diego, 3855 Health Sciences Dr, La Jolla, CA 92037; e-mail: rmckay@ucsd.edu.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/OP.20.00431.

AUTHOR CONTRIBUTIONS

Conception and design: Brittany M. Szymaniak, Lauren A. Facchini, Veda N. Giri, Emmanuel S. Antonarakis, Tomasz M. Beer, Daniel C. Danila, Daniel George, Julie N. Graff, Shilpa Gupta, Celestia S. Higano, Channing J. Paller, Charles J. Ryan, Mary-Ellen Taplin, Alicia K. Morgans, Heather H. Cheng, Rana R. McKay

Collection and assembly of data: Brittany M. Szymaniak, Lauren A. Facchini, Emmanuel S. Antonarakis, Tomasz M. Beer, Daniel C. Danila, Shilpa Gupta, Elisabeth Heath, Celestia S. Higano, Ana M. Molina, Akash Patnaik, Heather H. Cheng, Rana R. McKay

Data analysis and interpretation: Brittany M. Szymaniak, Lauren A. Facchini, Veda N. Giri, Tomasz M. Beer, Maria I. Carlo, Daniel C. Danila, Mallika Dhawan, Daniel George, Shilpa Gupta, Elisabeth Heath, Glenn Liu, Ana M. Molina, Akash Patnaik, Daniel P. Petrylak, Zachery Reichert, Matthew B. Rettig, Mary-Ellen Taplin, Jake Vinson, Young E. Whang, Heather H. Cheng, Rana R. McKay

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

B.M.S. and L.A.F. are co-first authors. A.K.M., H.H.C., and A.R.M. contributed equally to this work.

REFERENCES

1. Seyhan AA, Carini C: Are innovation and new technologies in precision medicine paving a new era in patients centric care? J Transl Med 17:114, 2019
2. Roos A, Byron SA: Genomics-enabled precision medicine for cancer. Cancer Treat Res 178:137-169, 2019
3. Zhang H, Klareskog L, Matussek A, et al: Translating genomic medicine to the clinic: Challenges and opportunities. Genome Med 11:9, 2019
4. Sachdev JC, Sandoval AC, Jahanzeb M: Update on precision medicine in breast cancer. Cancer Treat Res 178:45-80, 2019
5. Carlo MI, Giri VN, Paller CJ, et al: Evolving intersection between inherited cancer genetics and therapeutic clinical trials in prostate cancer: A white paper from the Germline Genetics Working Group of the Prostate Cancer Clinical Trials Consortium. JCO Precis Oncol 10.1200/PO.18.00060
6. Paller CJ, Antonarakis ES, Beer TM, et al: Germline genetic testing in advanced prostate cancer; practices and barriers: Survey results from the Germline Genetics Working Group of the Prostate Cancer Clinical Trials Consortium. Clin Genitourin Cancer 17:275-282.e1, 2019
7. Pritchard CC, Mateo J, Walsh MF, et al: Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med 375:443-453, 2016
8. Leongamornlert D, Saunders E, Dadaev T, et al: Frequent germline deleterious mutations in DNA repair genes in familial prostate cancer cases are associated with advanced disease. Br J Cancer 110:1663-1672, 2014
9. Isaacsson Velho P, Silberstein JL, Markowski MC, et al: Intraductal/ductal histology and lymphovascular invasion are associated with germline DNA-repair gene mutations in prostate cancer. Prostate 78:401-407, 2018
10. Abida W, Armenia J, Gopalan A, et al: Prospective genomic profiling of prostate cancer across disease states reveals germline and somatic alterations that may affect clinical decision making. JCO Precis Oncol 10.1200/PO.17.00029
11. Nicolosi P, Ledet E, Yang S, et al: Prevalence of germline variants in prostate cancer and implications for current genetic testing guidelines. JAMA Oncol 5: 523-528, 2019
12. Maiese DR, Keehn A, Lyon M, et al: Current conditions in medical genetics practice. Genet Med 21:1874-1877, 2019
13. US Bureau of Labor Statistics: Occupational employment statistics. www.bls.gov/oes/
14. Hoskovec JM, Bennett RL, Carey ME, et al: Projecting the supply and demand for certified genetic counselors: A workforce study. J Genet Couns 27:16-20, 2018
15. Bellcross CA, Kolor K, Goddard KA, et al: Awareness and utilization of BRCA1/2 testing among U.S. primary care physicians. Am J Prev Med 40:61-66, 2011
16. Plon SE, Cooper HP, Parks B, et al: Genetic testing and cancer risk management recommendations by physicians for at-risk relatives. Genet Med 13:148-154, 2011
17. Mahon SM: Errors in genetic testing: Common causes and strategies for prevention. Clin J Oncol Nurs 21:673-676, 2017
18. Cohen SA, Bradbury A, Henderson V, et al: Genetic counseling and testing in a community setting: Quality, access, and efficiency. Am Soc Clin Oncol Educ Book 39:e34-e44, 2019
19. Stoll K, Kubendran S, Cohen SA: The past, present and future of service delivery in genetic counseling: Keeping up in the era of precision medicine. Am J Med Genet C Semin Med Genet 178:24-37, 2018
20. Riconda D, Grubs RE, Campion MW, et al: Genetic counselor training for the next generation: Where do we go from here? Am J Med Genet C Semin Med Genet 178:38-45, 2018
21. Giri VN, Hyatt C, Gomella LG: Germline testing for men with prostate cancer: Navigating an expanding new world of genetic evaluation for precision therapy and precision management. J Clin Oncol 37:1455-1459, 2019
22. Daly MB, Pilarski R, Yurgelun MB, et al: NCCN guidelines insights: Genetic/familial high-risk assessment: Breast, ovarian, and pancreatic, version 1.2020. J Natl Compr Canc Netw 18:380-391, 2020
23. Tandy-Connor S, Guiltinan J, Krempely K, et al: False-positive results released by direct-to-consumer genetic tests highlight the importance of clinical confirmation testing for appropriate patient care. Genet Med 20:1515-1521, 2018
24. Riley BD, Culver JO, Skrzynia C, et al: Essential elements of genetic cancer risk assessment, counseling, and testing: Updated recommendations of the National Society of Genetic Counselors. J Genet Couns 21:151-161, 2012
25. Mandelker D, Donoghue M, Talukdar S, et al: Germline-focussed analysis of tumour-only sequencing: Recommendations from the ESMO Precision Medicine Working Group. Ann Oncol 30:1221-1231, 2019
26. Giri VN, Knudsen KE, Kelly WK, et al: Implementation of germline testing for prostate cancer: Philadelphia Prostate Cancer Consensus Conference 2019. J Clin Oncol 10.1200/JCO.20.00046 [epub ahead of print on June 9, 2020]
27. Cheng H, Powers J, Schaffer K, et al: Practical methods for integrating genetic testing into clinical practice for advanced prostate cancer. Am Soc Clin Oncol Educ Book 38:372-381, 2018
28. Mersch J, Brown N, Pirzadeh-Miller S, et al: Prevalence of variant reclassification following hereditary cancer genetic testing. JAMA 320:1266-1274, 2018
29. Macklin S, Durand N, Atwal P, et al: Observed frequency and challenges of variant reclassification in a hereditary cancer clinic. Genet Med 20:346-350, 2018
30. Puzanov I, Diab A, Abdallah K, et al: Managing toxicities associated with immune checkpoint inhibitors: Consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. J Immunother Cancer 5:95, 2017
31. Hryniewicki AT, Wang C, Shatsky RA, et al: Management of immune checkpoint inhibitor toxicities: A review and clinical guideline for emergency physicians. J Emerg Med 55:489-502, 2018
32. West AH, Knollman H, Dugan J, et al: Hematologic toxicity in BRCA1 and BRCA2 mutation carriers during chemotherapy: A retrospective matched cohort study. Cancer Med 8:5609-5618, 2019
33. Croyle RT, Achilles JS, Lerman C: Psychologic aspects of cancer genetic testing: A research update for clinicians. Cancer 80:569-575, 1997(3; suppl)
34. Meiser B: Psychological impact of genetic testing for cancer susceptibility: An update of the literature. Psycho-oncology 14:1060-1074, 2005
35. Greenberg S, Slager S, Neil BO, et al: What men want: Qualitative analysis of what men with prostate cancer (PCa) want to learn regarding genetic referral, counseling, and testing. Prostate 80:441-450, 2020
36. Buchanan AH, Rahm AK, Williams JL: Alternate service delivery models in cancer genetic counseling: A mini-review. Front Oncol 6:120, 2016
37. Hnatiuk MJ, Noss R, Mitchell AL, et al: The current state of genetic counseling assistants in the United States. J Genet Couns 28:962-973, 2019
38. McCuaig JM, Armel SR, Care M, et al: Next-generation service delivery: A scoping review of patient outcomes associated with alternative models of genetic counseling and genetic testing for hereditary cancer. Cancers (Basel) 10:435, 2018
39. Hann KEJ, Freeman M, Fraser L, et al: Awareness, knowledge, perceptions, and attitudes towards genetic testing for cancer risk among ethnic minority groups: A systematic review. BMC Public Health 17:503, 2017
40. Shields AE, Burke W, Levy DE: Differential use of available genetic tests among primary care physicians in the United States: Results of a national survey. Genet Med 10:404-414, 2008

41. Childers KK, Maggard-Gibbons M, Macinko J, et al: National distribution of cancer genetic testing in the United States: Evidence for a gender disparity in hereditary breast and ovarian cancer. JAMA Oncol 4:876-879, 2018
42. Pritchard CC: New name for breast-cancer syndrome could help to save lives. Nature 571:27-29, 2019
43. Rauscher EA, Dean M: "I've just never gotten around to doing it": Men's approaches to managing BRCA-related cancer risks. Patient Educ Couns 101:340-345, 2018
44. Mohler JL, Srinivas S, Antonarakis ES, et al: Prostate cancer, version 1.2020, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 17: 479-505, 2020
45. Giri VN, Knudsen KE, Kelly WK, et al: Role of genetic testing for inherited prostate cancer risk: Philadelphia Prostate Cancer Consensus Conference 2017. J Clin Oncol 36:414-424, 2018
46. Sanda MG, Cadeddu JA, Kirkby E, et al: Clinically localized prostate cancer: AUA/ASTRO/SUO guideline. Part I: Risk stratification, shared decision making, and care options. J Urol 199:683-690, 2018
47. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 17:405-424, 2015
48. Adam MP, Ardinger HH, Pagon RA (eds): GeneReviews [Internet]. https://www.ncbi.nlm.nih.gov/books/NBK5191/
49. American College of Medical Genetics: Genetic Susceptibility to Breast and Ovarian Cancer: Assessment, Counseling and Testing Guidelines. https://www.ncbi.nlm.nih.gov/books/NBK56955/

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Practical Considerations and Challenges for Germline Genetic Testing in Patients With Prostate Cancer: Recommendations From the Germline Genetics Working Group of the PCCTC

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/op/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Brittany M. Szymaniak
Honoraria: Invitae Corporation, Urogpo
Consulting or Advisory Role: Clovis Oncology
Uncompensated Relationships: Urogpo

Veda N. Giri
Stock and Other Ownership Interests: Novopyxis (I)
Speakers' Bureau: Janssen

Emmanuel S. Antonarakis
Honoraria: Sanofi, Dendreon, Medivation, Janssen Biotech, Essa, Astellas Pharma, Merck, AstraZeneca, Clovis Oncology
Consulting or Advisory Role: Sanofi, Dendreon, Janssen Biotech, Essa, Merck, AstraZeneca, Clovis Oncology, Lilly, Bayer
Research Funding: Janssen Biotech (Inst), Johnson & Johnson (Inst), Sanofi (Inst), Dendreon (Inst), Aragon Pharmaceuticals (Inst), Exelixis (Inst), Millennium (Inst), Genentech (Inst), Novartis (Inst), Astellas Pharma (Inst), Tokai Pharmaceuticals (Inst), Merck (Inst), AstraZeneca (Inst), Clovis Oncology (Inst), Constellation Pharmaceuticals (Inst)
Patents, Royalties, Other Intellectual Property: Co-inventor of a biomarker technology that has been licensed to Qiagen
Travel, Accommodations, Expenses: Sanofi, Dendreon, Medivation

Tomasz M. Beer
Stock and Other Ownership Interests: Salarius Pharmaceuticals, Arvinas
Consulting or Advisory Role: Astellas Pharma, AstraZeneca, Bayer, Bristol Myers Squibb, Clovis Oncology, GlaxoSmithKline, Novartis, Pfizer, Arvinas, Tolero Pharmaceuticals
Research Funding: Alliance Foundation Trials (Inst), Astellas (Inst), Boehringer Ingelheim (Inst), Corcept Therapeutics (Inst), Endocyte (Inst), Janssen Research & Development (Inst), Harpoon Therapeutics (Inst), Medivation (Inst), Sotio (Inst), Theraclone Sciences (Inst), Zenith Epigenetics (Inst)

Maria I. Carlo
Consulting or Advisory Role: Pfizer
Other Relationship: Prostate Cancer Foundation, Robert Wood Johnson Foundation

Daniel C. Danila
Honoraria: Angle, Bayer, ScreenCell, Janssen Oncology, Pfizer, AxImmune, Clovis Oncology, Astellas Pharma
Consulting or Advisory Role: Angle, Bayer, Sanador, AxImmune, Pfizer, Clovis Oncology, Astellas Pharma, Janssen Scientific Affairs
Research Funding: Prostate Cancer Foundation, Genentech, Janssen Research Development (Inst)
Patents, Royalties, Other Intellectual Property: Gene expression profile associated with prostate cancer
Travel, Accommodations, Expenses: Cambridge Healthtech Institute, Prostate Cancer Foundation, ScreenCell, StopCancer, American Austrian Open Medical Institute, Janssen Biotech, Genzyme, Pfizer, Janssen Scientific Affairs, Astellas Pharma

Daniel George
Leadership: Capio BioSciences
Honoraria: Sanofi, Bayer, Exelixis, EMD Serono, OncLive, Pfizer, UroToday, Acceleron Pharma, American Association for Cancer Research, Axess Oncology, Janssen Oncology, Millennium Medical Publishing
Consulting or Advisory Role: Bayer, Exelixis, Pfizer, Sanofi, Astellas Pharma, Innocrin Pharma, Bristol Myers Squibb, Genentech, Janssen, Merck Sharp & Dohme, Myovant Sciences, AstraZeneca, Michael J. Hennessy Associates, Vizuri Health Sciences
Speakers' Bureau: Sanofi, Bayer, Exelixis
Research Funding: Exelixis (Inst), Janssen Oncology (Inst), Novartis (Inst), Pfizer (Inst), Astellas Pharma (Inst), Bristol Myers Squibb (Inst), Acerta Pharma (Inst), Bayer (Inst), Dendreon (Inst), Innocrin Pharma (Inst), Calithera Biosciences (Inst), Sanofi/Aventis (Inst)
Travel, Accommodations, Expenses: Bayer, Exelixis, Merck, Pfizer, Sanofi, Janssen Oncology, UroToday

Julie N. Graff
Honoraria: Janssen Oncology, Valeant/Dendreon, Bayer, Sanofi, Astellas Medivation
Consulting or Advisory Role: Exelixis
Speakers' Bureau: i3 CME
Research Funding: Sanofi (Inst), Medivation (Inst), Merck Sharp & Dohme (Inst), Janssen Oncology (Inst)
Patents, Royalties, Other Intellectual Property: Oncoresponse: Exceptional responders
Travel, Accommodations, Expenses: Bayer, Merck Sharp & Dohme, Clovis Oncology, Sanofi

Shilpa Gupta
Stock and Other Ownership Interests: Nektar
Honoraria: Janssen Oncology, AstraZeneca, Exelixis, Bristol Myers Squibb, Merck Sharp & Dohme, Seattle Genetics, Pfizer
Speakers' Bureau: Bristol Myers Squibb, Janssen Oncology, Exelixis
Research Funding: Merck, Pfizer, Bristol Myers Squibb, Seattle Genetics

Elisabeth Heath
Honoraria: Bayer, Dendreon, Sanofi, Seattle Genetics
Consulting or Advisory Role: Agensys, Bayer, Dendreon
Speakers' Bureau: Sanofi
Research Funding: Tokai Pharmaceuticals (Inst), Seattle Genetics (Inst), Agensys (Inst), Dendreon (Inst), Genentech (Inst), Millennium (Inst), Celldex (Inst), Inovio Pharmaceuticals (Inst), Celgene (Inst), Zenith Epigenetics (Inst), Merck (Inst), AstraZeneca (Inst), Esanik (Inst), Zenith Epigenetics (Inst), Oncolys BioPharma (Inst), Curemeta (Inst), Bristol Myers Squibb (Inst), eFFECTOR Therapeutics (Inst), Fortis (Inst), Astellas Pharma (Inst), Medivation (Inst), Ignyta (Inst), Synta (Inst), Caris Life Sciences (Inst), Boehringer Ingelheim (Inst), GlaxoSmithKline (Inst), Merck Sharp & Dohme (Inst), Plexxikon (Inst), Corcept Therapeutics (Inst), Infinity Pharmaceuticals (Inst), Bayer (Inst), Modra Pharmaceuticals (Inst), Pellficure Pharmaceuticals (Inst), Champions Oncology (Inst), AIQ Solutions (Inst), Novartis Pharmaceuticals (Inst), Janssen Research & Development (Inst), Mirati Therapeutics (Inst), Peloton (Inst), Daiichi Sankyo (Inst), Calibr (Inst), Eisai (Inst), Pharmacyclics (Inst), FivePrime Therapeutics (Inst)
Travel, Accommodations, Expenses: Agensys, Bayer, Sanofi
Other Relationship: Caris Centers of Excellence

Celestia S. Higano
Honoraria: Astellas Pharma
Consulting or Advisory Role: Bayer, Ferring, Clovis Oncology, Blue Earth Diagnostics, Janssen, Hinova, Pfizer, AstraZeneca, Carrick Therapeutics, Novartis, Merck Sharp & Dohme
Research Funding: Aragon Pharmaceuticals (Inst), AstraZeneca (Inst), Medivation (Inst), Emergent BioSolutions (Inst), Bayer (Inst), Pfizer (Inst), Roche (Inst), Astellas Pharma (Inst), Clovis Oncology (Inst), Ferring Pharmaceuticals (Inst), eFFECTOR Therapeutics (Inst)
Travel, Accommodations, Expenses: Bayer, Clovis Oncology, Blue Earth Diagnostics, Ferring, Pfizer, Hinova Pharmaceuticals, Janssen Oncology, Novartis, Merck Sharp & Dohme, Carrick Therapeutics

Glenn Liu
Employment: AIQ Solutions
Leadership: AIQ Solutions
Stock and Other Ownership Interests: AIQ Solutions
Consulting or Advisory Role: Novartis, Exelixis, Tricon Pharmaceuticals
Research Funding: Johnson & Johnson (Inst), Novartis (Inst), Madison Vaccines, Pfizer, Tracon Pharma
Patents, Royalties, Other Intellectual Property: I have a patent pending titled "System and method for evaluation of disease burden," which provides a novel method to identify and quantitate treatment response (Inst)
Travel, Accommodations, Expenses: AIQ Solutions, Tracon Pharma

Ana M. Molina
Honoraria: ASCO
Consulting or Advisory Role: Eisai, Exelixis, Novartis, Janssen

Channing J. Paller
Consulting or Advisory Role: Dendreon, Omnitura
Research Funding: Lilly (Inst)

Akash Patnaik
Stock and Other Ownership Interests: Gilead, Genentech, Merck, Prime Oncology, Jounce Therapeutics, Exelixis
Consulting or Advisory Role: Jounce Therapeutics, Exelixis, Guidepoint, Gerhson Lehrman Group
Research Funding: Bristol Myers Squibb (Inst), Progenics (Inst), Clovis Oncology (Inst)
Travel, Accommodations, Expenses: Bristol Myers Squibb, Prime Oncology, Exelixis

Daniel P. Petrylak
Stock and Other Ownership Interests: Bellicum Pharmaceuticals, TYME
Consulting or Advisory Role: Bayer, Exelixis, Pfizer, Roche, Astellas Pharma, AstraZeneca, Lilly, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Clovis Oncology, Incyte, Janssen, Pharmacyclics, Seattle Genetics, Urogen Pharma, Advanced Accelerator Applications, Ipsen
Research Funding: Progenics (Inst), Sanofi (Inst), Endocyte (Inst), Genentech (Inst), Merck (Inst), Astellas Medivation (Inst), Novartis (Inst), AstraZeneca (Inst), Bayer (Inst), Lilly (Inst), Innocrin Pharma (Inst), MedImmune (Inst), Pfizer (Inst), Roche (Inst), Seattle Genetics (Inst), Clovis Oncology (Inst), Bristol Myers Squibb (Inst), Advanced Accelerator Applications (Inst)
Expert Testimony: Celgene, Sanofi

Zachery Reichert
Consulting or Advisory Role: Dendreon
Research Funding: AstraZeneca (Inst)

Matthew Rettig
Consulting or Advisory Role: Johnson & Johnson, Ambrx, Amgen, Clovis
Speakers' Bureau: Johnson & Johnson, Bayer
Research Funding: Novartis (Inst), Astellas Medivation (Inst), Johnson & Johnson (Inst)
Patents, Royalties, Other Intellectual Property: I am a co-inventor on a patent for novel inhibitors of the N-terminal domain of the AR. There are no commercial partnerships as of yet.
Travel, Accommodations, Expenses: Johnson & Johnson

Charles J. Ryan
Honoraria: Janssen Oncology, Bayer
Consulting or Advisory Role: Bayer, Dendreon, AAA, Myovant Sciences, Clovis Oncology (Inst), Roivant, Clovis Oncology (Inst), Sanofi Genzyme (Inst)

Mary-Ellen Taplin
Honoraria: Janssen-Ortho, Clovis Oncology, Astellas Pharma, Incyte, UpToDate, Research to Practice, Pfizer, Bayer, Amgen, AstraZeneca, Progenics, Guidepoint Global, Celegen, Merck, GSK, Myovant, Roivant Sciences
Consulting or Advisory Role: Janssen-Ortho, Bayer, Guidepoint Global, Best Doctors, UpToDate, Clovis Oncology, Research to Practice, Myovant Sciences, Incyte, Pfizer, AstraZeneca, Arcus (I)
Research Funding: Janssen-Ortho (Inst), Medivation (Inst), Bayer (Inst), Pfizer (Inst)
Travel, Accommodations, Expenses: Medivation, Janssen Oncology, Tokai Pharmaceuticals, Astellas Pharma, Incyte, Pfizer, Clovis Oncology, Bayer

Young E. Whang
Research Funding: Astellas Pharma (Inst), Clovis Oncology (Inst), Constellation Pharmaceuticals (Inst), Amgen (Inst)

Alicia K. Morgans
Honoraria: Genentech, Janssen, Sanofi, AstraZeneca, Astellas Scientific and Medical Affairs, Astellas Colombia, Janssen Oncology, Bayer
Consulting or Advisory Role: Genentech, AstraZeneca, Sanofi, Bayer, Astellas Pharma, Janssen, Advanced Accelerator Applications, Myovant Sciences
Research Funding: Bayer, Seattle Genetics/Astellas, Genentech, AstraZeneca, Astellas Scientific and Medical Affairs
Travel, Accommodations, Expenses: Sanofi

Heather H. Cheng
Consulting or Advisory Role: AstraZeneca (Inst)
Research Funding: Sanofi (Inst), Janssen (Inst), Clovis Oncology (Inst), Color Foundation (Inst), Fred Hutchinson Cancer Research Center (Inst)

Rana R. McKay
Consulting or Advisory Role: Janssen, Novartis, Tempus, Exelixis, Pfizer, Bristol Myers Squibb, Astellas Medivation, Dendreon, Vividion, Bayer, Sanofi
Research Funding: Pfizer (Inst), Bayer (Inst)

Heather H. Cheng
Research Funding: Inovio Pharmaceuticals, Sanofi, Astellas Medivation, Janssen, Clovis Oncology, Color Foundation (Inst)

No other potential conflicts of interest were reported.

Current Oncology Reports (2020) 22: 5
https://doi.org/10.1007/s11912-020-0863-6

GENITOURINARY CANCERS (DP PETRYLAK AND JW KIM, SECTION EDITORS)

Genetic Testing in Prostate Cancer

Alexandra O. Sokolova [1,2,3] · Heather H. Cheng [1,2]

Published online: 23 January 2020

Abstract
Purpose of Review This review summarizes recent advances in prostate cancer (PCa) genetics.
Recent Findings Upwards of 20% of metastatic castration-resistant prostate tumors (mCRPC) carry homologous recombination (HR) repair gene mutations, of which ~ 10% are germline (inherited). Another ~ 5% exhibit microsatellite instability (MSI-H) and/or mismatch repair deficiency (MMRd). Pembrolizumab is approved for tumors with MMRd, thus patients with mCRPC and MMRd are candidates for pembrolizumab. Emerging data indicate that platinum chemotherapy and poly ADP-ribose polymerase inhibitors (PARPi) are effective in PCa exhibiting HR deficiency. NCCN guidelines now recommend germline and somatic tumor testing in specific clinical scenarios due to treatment and family implications.
Summary Genetic testing in PCa patients may inform prognosis, treatment options, and have implications for family counseling. PARPi, platinum chemotherapy, and immune checkpoint inhibitors are promising targeted therapies for PCa with specific molecular features. Therapeutic advances, along with importance to relatives, are driving genetic testing in prostate cancer.

Keywords Prostate cancer · Genetics · BRCA · PARPi · Germline testing

Introduction

Prostate cancer has a significant heritable component. In the past few years, substantial strides have been made in understanding genetic factors influencing prostate cancer susceptibility. Many of the recent discoveries have extended beyond common single-nucleotide polymorphisms (SNPs) to high and moderate penetrance genetic variants, alongside new precision-directed therapeutic implications that are leading to shifts in research and practice.

More than 100 susceptibility loci for prostate cancer have been identified with GWAS (genome-wide association studies), accounting for ~ 33% of familial prostate cancer risks [1–7]. Many variants identified were high prevalence and low-penetrance, and were not clinically used to differentiate risk of aggressive from indolent prostate cancer [7]. The germline *HOXB13 G84E* variant was established in 2012 as a susceptibility loci that significantly increased prostate cancer risk through study of families with multiple cases of prostate cancer [8]. Germline testing of unselected prostate cancer patients showed overall low prevalence of germline pathogenic or likely pathogenic variants (hereafter referred as mutations) in *BRCA2*; 1.2% among men were diagnosed before 65 years old [9, 10]. Prior to 2016, clinical germline testing for prostate cancer risk was not pervasive.

The Molecular Landscape of Metastatic Prostate Cancer

Substantial changes came with a Stand Up To Cancer-Prostate Cancer Foundation Prostate Cancer Dream Team study that sequenced metastatic prostate cancer biopsies and provided molecular characterization of later evolutionary stages of tumorigenesis [11]. A notable finding was that alterations in *BRCA2*, *BRCA1*, and *ATM* were observed in 19.3% (29/150) of metastatic tumors—a much higher frequency compared with localized disease [9, 11]. Eight percent (12/150) of patients with metastatic prostate cancer had pathogenic germline alterations [11].

This article is part of the Topical Collection on *Genitourinary Cancers*

✉ Heather H. Cheng
hhcheng@uw.edu

[1] Department of Medicine, University of Washington, Washington, USA

[2] Clinical Research Division, Fred Hutchinson Cancer Research Center, 825 Eastlake Ave E, Seattle, WA 98109, USA

[3] VA Puget Sound Health Care System, 1660 S Columbian Way, Seattle, WA 98108, USA

Prevalence of Germline Mutations in Metastatic Prostate Cancer

In 2016, Pritchard et al. reported a study of germline sequencing in 692 men with metastatic prostate cancer, unselected for family history or age at diagnosis, and found that 11.8% (82/692) had germline DNA repair alterations compared with 4.6% (23/499) among men with localized prostate cancer from the Cancer Genome Atlas (TCGA), and 2.7% (1434/53,105) in persons without a known cancer diagnosis (EXAC) [12••]. A subsequent cross-sectional study by Nicolosi et al. evaluated 3607 men with a personal history of prostate cancer who underwent germline genetic testing between 2013 and 2018. The study found that 4.74% of patients with prostate cancer had g*BRCA2* mutations, 2.88% g*CHEK2*, 2.03% g*ATM*, 1.25% g*BRCA1*, 1.12% g*HOXB13*, 0.69% g*MSH2*, and 0.56% g*PALB2* gene mutations [13]. The higher than previously recognized prevalence of DNA repair gene mutations led to changes in clinical testing guidelines.

Emerging data suggest that patients with ductal and intraductal prostate cancer carcinoma have higher risk of having microsatellite instability [14–17] and germline homologous recombination repair mutations [17–20]. Taylor et al. performed whole exome sequencing of prostate cancer tumors from 14 patients with castration-sensitive localized prostate cancer and g*BRCA2* mutations, and showed that these tumors harbor increased genomic instability, and their mutation profiles resemble metastatic tumor [18]. A case study of patients with ductal histology prostate carcinoma showed that 49% (25/51) had DNA repair gene alterations, including 20% (10/51) with germline alterations. Somatic tumor sequencing of this patient cohort reported that 14% (7/51) tumors had mismatch repair gene alterations and 31% (16/51) in homologous recombination repair genes [17].

Collectively, these studies suggest that germline DNA repair mutations are present in substantial percentages in specific populations, (1) prostate cancer patients with metastatic disease, (2) those with a family history suggestive of inherited cancer predisposition, (3) ductal and intraductal histologic subtypes. NCCN guidelines for prostate cancer now recommend offering germline genetic testing to men in these groups (Table 1) [21, 22].

Family Impact of Germline Testing

Germline testing in men with prostate cancer can potentially benefit the patient in informing treatment options, and if a mutation is identified, may also guide screening of other cancers and have family implications for cascade genetic testing (testing of close relatives for the same germline mutation). Early cancer detection strategies and preventive measures may be available to relatives identified to have same germline mutations. Cascade family testing can be valuable for family members, but unfortunately cascade family testing is currently underperformed, and strategies to overcome barriers, such as lack of knowledge, family communication, lack of access to genetic services, and cost of testing, are needed.

Table 1 Family history for prostate cancer patients

Family history criteria
Family history of high-risk germline mutations (e.g., *BRCA1/2*, Lynch syndrome)
Brother or father or multiple family members diagnosed with prostate cancer (but not clinically localized grade group 1) at < 60 years or who died from prostate cancer
Ashkenazi Jewish ancestry
≥ 3 cancers on same side of family, especially diagnosed at age ≤ 50 years, bile duct, breast, colorectal, endometrial, gastric, kidney, melanoma, ovarian, pancreatic, prostate (but not clinically localized grade group 1), small bowel, or urothelial

The NCCN guidelines for Genetic/Familial High-Risk Assessment for Breast and Ovarian Cancer [23] recommend breast cancer screening starting at age 25 years for female relatives and age 36 years for male relatives with deleterious g*BRCA1/2* mutations. g*BRCA1/2* female carriers should discuss with their health care provider risk reduction mastectomy and salpingo-oophorectomy, which is typically recommended between 35, 36, 37, 38, 39, 40 years old, and upon completion of childbearing.

Male relatives with g*BRCA2 and* g*BRCA1* mutations may be at increased risk of cancers such as male breast, pancreatic, colon, and prostate. A study of 173 breast-ovarian cancer families with g*BRCA2* mutations showed 4.7- to 8.6-fold increased risks of prostate cancer with cumulative risk of 20–33% in US carriers by the age of 70 years [24]. A study of 913 male g*BRCA1* mutation carriers reported that g*BRCA1* mutation increases the relative risk of prostate cancer by 3.75-fold and results in an 8.6% cumulative risk by age 65 [25].

The IMPACT study (Identification of Men with a Genetic Predisposition to Prostate Cancer: Targeted screening in g*BRCA1/2* mutation carriers and controls) conducted yearly PSA screening in families with known g*BRCA1/2* mutations [26, 27]. The study enrolled 2932 men with no personal history of prostate cancer, 919 g*BRCA1* carriers, 902 g*BRCA2*, 497 g*BRCA2* noncarriers, and 709 g*BRCA1* noncarriers. Preliminary results reported after 3 years of follow-up showed overall 21% positive predictive value (PPV) of PSA > 0.3 ng/ml with 31% PPV in g*BRCA2* carriers and 18% in *gBRCA2* noncarriers; and 23% in *gBRCA1* carriers and 15% in g*BRCA1* noncarriers. PPV of prostate biopsy, initiated when PSA > 3.0 ng/ml, was 39% in g*BRCA2* carriers and 28% in g*BRCA2* noncarriers, but no significant difference was detected between g*BRCA1* carriers and g*BRCA1* noncarriers. g*BRCA2* carriers had higher incidence of prostate cancer diagnosed at younger age and

with more aggressive disease characteristics compared with g*BRCA2* noncarriers. The results for g*BRCA1* carriers were not definitive, and further investigation is needed. The number needed to screen to detect one clinically significant prostate cancer was 60 for g*BRCA2* carriers ages 40–54 years and 13 for carriers ages 55–69 years. Thus, the results from IMPACT suggest annual PSA screening for g*BRCA2* mutation carriers between age 40 and 69, using PSA cutoff of 3 ng/ml [27]. Studies evaluating predictive value of lower PSA cutoff and prostate MRI are ongoing (e.g., www.clinicatrials.gov, NCT03805919, NCT01990521).

Prognostic Impact of DNA Repair Gene Mutations

Prostate cancer patients may benefit from germline and/or somatic genetic testing to inform disease prognosis and treatment decisions, with somatic testing being potentially more relevant for treatment decisions. Several studies showed that germline *BRCA1/2* mutations are associated with poor prognosis and worse outcomes in prostate cancer. Castro et al. showed that prostate cancer patients with g*BRCA1/2* mutations were more likely to have a Gleason score ≥ 8, T3/4 stage, nodal involvement, and metastases at the time of diagnosis compared with noncarriers. Moreover, g*BRCA1/2* carriers had shorter cancer-specific survival (CSS) compared with noncarriers (15.7 vs 8.6 years) [28]. g*BRCA*1/2 carriers with localized prostate cancer have worse outcomes after conventional treatment with surgery or radiation compared with noncarriers, 5-year metastasis free survival 72% vs 94%, 5 year CSS 76% vs 97% [29]. A retrospective case study by Na et al. found that proportion of men carrying g*BRCA1/2* or g*ATM* mutations was significantly higher in men who died from prostate cancer compared with men with localized disease (6.07% vs 1.44%). This study also showed that among patients with lethal prostate cancer rate of g*BRCA1/2* and g*ATM* mutations was higher in patients who died younger, 10% among those who died < 60years, 9% for age of death 61–65; 8% 66–70 years, 4% 71–75 years, and 2.97% among those who died > 75 years old [30•]. The prospective PROREPAIR-B found that g*BRCA2* status is an independent prognostic factor for CSS in metastatic castration-resistant prostate cancer (mCRPC) patients (17.4 vs 33.2 months, $p = 0.027$) [31••].

Somatic DNA repair gene mutations are present in about 8–10% of localized prostate cancer cases and 20–25% of mCRPC cases, and Marshall et al. reported that presence in localized disease is associated with higher Gleason grade group (≥ 3) and more advance clinical stage (≥ cT3 disease) at the time of diagnoses [32].

Recommendations for Genetic Testing in Prostate Cancer

Based on these and other studies, NCCN guidelines for Prostate Cancer recommend offering germline testing, ideally with genetic counseling access, to the following groups of prostate cancer patients [22]:

1. Men with high-risk, very-high risk localized prostate cancer
2. Men with metastatic prostate cancer
3. Men with intraductal histology
4. Men with Ashkenazi Jewish ancestry
5. Men meeting family history criteria (see Table 1)

Somatic tumor sequencing should also be considered in prostate cancer patients especially with advanced disease. Sequencing of tumor metastatic biopsies is preferred when available, as tumor clones evolve over time, and primary prostate cancer tissue might miss alterations developed later in the disease course. Men should also be counseled that somatic tumor testing could potentially suggest presence of a germline mutation, and if the case, referral to genetic counseling to discuss dedicated germline testing would be advised. NCCN guidelines for Prostate Cancer recommend that germline and somatic testing panels should include Lynch syndrome associated genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2)* and homologous recombination genes (*BRCA1/2*, *ATM*, *PALB2*, *CHEK2*) [21, 22]. Other genes might be appropriate for testing in certain scenarios, such as potential enrollment into clinical trials, where significance of newer gene/mutations as biomarkers for new treatments are being explored.

Treatment Implications of Genetic Testing

Advanced Disease

Targeted therapies are being investigated in clinical trials for prostate cancer patients with specific DNA repair gene alterations in tumor and/or germline. At present, the treatment implications of genetic testing are arguably greatest in metastatic disease, as this is the disease space with the majority of therapeutic clinical trials.

Some studies are available in earlier disease states of prostate cancer and more are expected to follow. Patients with homologous DNA repair mutations are candidates for clinical trials using poly ADP-ribose polymerase inhibitors (PARPi) and/or platinum chemotherapy, and novel combinations. There are several ongoing clinical trials evaluating the role of these agents as monotherapy or in various combination therapies in different stages of prostate cancer (e.g., www.clinicatrials.gov, NCT02975934, NCT02952534, NCT02854436, NCT02987543, NCT03413995). Below is a

summary of current data on targeted therapy in prostate cancer patients with DNA repair gene mutations, i.e., immunotherapy, PARPi, platinum chemotherapy.

Immunotherapy Pembrolizumab received the first tumor agnostic FDA approval in 2017 for metastatic solid tumors with microsatellite instability (MSI-H) and mismatch repair deficiency (MMRd) [33, 34]. About 5% of mCRPC cases are estimated to be MSI-H/MMRd and would qualify for treatment with pembrolizumab [35•, 36–38]. In a single institution case series of 1033 prostate tumors undergoing next generation sequencing, 3.1% (32/1033) were found to be MSI-H/MMRd, 78% (25/32) tumors had somatic mutations, and 22% (7/32) were found to have germline Lynch-associated mutations [35•]. Somatic and germline testing for MSI-H/MMRd is recommended in certain prostate cancer patient populations (see above) and has direct clinical implications as MSI-H/MMRd patients are eligible for pembrolizumab in second line of mCRPC treatment.

PARPi Patients with DNA repair mutations have higher response rates to PARPi and platinum chemotherapy [39]. The clinical activity of PARPi in prostate cancer was first reported in the TOPARP-A trial (Trial of Olaparib in Patients with Advanced Castrate Resistant Prostate Cancer), which evaluated olaparib in mCRPC patients who failed multiple lines of therapy (98% received prior abiraterone or enzalutamide, 58% cabazitaxel) [40]. TOPARP-A reported that 88% (14/16) of patients with DNA repair mutations had response to olaparib therapy, where response was defined as a reduction in the PSA by 50% (PSA_{50}), a RECIST-defined objective response rate or circulating tumor cell reduction. Only 2 out 32 patients without DNA repair gene alterations responded to olaparib in TOPARP-A trial. As a result of this trial, olaparib received FDA breakthrough therapy designation in January 2016 for patients with *BRCA2*-, *BRCA1*-, or *ATM*-mutated mCRPC who had received prior taxane and either enzalutamide or abiraterone.

The phase 2 TRITON2 (NCT02952534) study evaluated rucaparib in mCRPC patients with homologous recombination gene mutation progressing after 1–2 lines of androgen receptor–directed therapy and 1 prior line of taxane. Preliminary results demonstrated that among *BRCA1/2* carries 44% (11/25) had radiographic response, and 51% (23/45) had PSA_{50} response [41••]. Based on these results, FDA granted rucaparib breakthrough designation in October 2018 [42].

The phase 2 TOPARP-B is a trial of PARPi in mCRPC patients with DNA damage repair alterations progressing after at least one taxane ($n = 98$) [43••]. The overall median progression-free survival (mPFS) was 5.4 months. Subgroup analyses per altered gene indicated following response rates (defined as in TOPARP-A study), *BRCA1/2* 83% (25/30; mPFS 8.1 months); *PALB2* 57% (4/7; mPFS 5.3 months); *ATM* 37% (7/19; mPFS 6.1 months); *CDK12* 25% (5/20; mPFS 2.9 months); other (*ATRX*, *CHEK1*, *CHEK2*, *FANCA*, *FANCF*, *FANCG*, *FANCI*, *FANCM*, *RAD50*, *WRN*) 20% (4/20; mPFS 2.8 months). The highest PSA_{50} response rates were observed in the *BRCA1/2* (22/30; 73%) and *PALB2* (4/6; 67%) mutated subgroups.

The first phase 3 randomized clinical trial evaluating PARPi in mCRPC was recently reported [44••]. PROfound enrolled mCRPC patients who progressed on abiraterone or enzalutamide and had mutations in homologous recombination DNA repair genes, identified by tumor sequencing; cohort A, patients with *BRCA1/2* and *ATM* mutations; cohort B, patients with mutations in other homologous recombination repair genes. Patients were randomized to olaparib 300 mg BID or physician's choice of enzalutamide or abiraterone. The results showed improved radiographic PFS (rPFS) in the olaparib arm of cohort A (7.39 vs 3.55 months, homologous recombination (HR) 0.34 $p < 0.001$), with objective response rate of 33.3% in olaparib and 2.3% in physician's choice arm of cohort A (OR 20.86 $p < 0.001$). Despite the crossover design, overall survival (OS) was 18.5 months in olaparib arm compared with 15.11 months in abiraterone/enzalutamide arm of cohort A, although statistical significance was not reached at time of initial reporting. There was also rPFS benefit in combined cohorts A and B, 5.82 months in olaparib arm vs 3.52 months in physician's choice arm (HR 0.49 $p < 0.001$). We anticipate that the FDA will approve olaparib for subset of mCRPC patients on the basis of the PROfound trial results.

Table 2 summarizes currently available study results reporting response rates to PARPi in prostate cancer.

Platinum chemotherapy Platinum chemotherapy has been proven to be effective in *BRCA1/2* mutated breast and ovarian cancers [49, 50]. Our single institution retrospective case series showed that 3/3 prostate cancer patients with biallelic inactivation of *BRCA2* had exceptional response to platinum chemotherapy after progressing on several therapies [51]. The findings were supported by a retrospective study that showed 75% (6/8) of mCRPC patients with *gBRCA2* mutation had PSA_{50} response to platinum chemotherapy compared with 17% (23/133) of mCRPC patients without g*BRCA2* mutations [52].

Localized Disease

In an active surveillance cohort, patients with localized prostate cancer and g*BRCA2*, g*BRCA1*, or g*ATM* mutations were more likely to experience grade reclassification compared with non-mutation carriers [53]. Further studies are warranted, but these data suggest that this group of patients will be monitored closely, ideally on a clinical trial, or consider a definitive treatment approach. The role of PARPi in localized prostate

Table 2 Response to PARPi in mCRPC patients stratified by HR gene mutations

Study	Agent used	Response measured by	Number of patients responded to PARPi by mutation status				
			BRCA1/2	*ATM*	*CDK12*	Other HRD mut	No HRD mut
PROfound, Hussain et al. [44••]	Olaparib vs abiraterone/enzalutamide	Imaging rPFS (months)	84/162 vs 42/83 7.39 vs 3.55		~3/94 vs ~4/48		N/A
TOPARP-A, Mateo et al. [40]	Olaparib	Imaging PSA_{50} CTC	8/8	4/5	N/A	2/3	2/33
TOPARP-B, Mateo et al. [43••]	Olaparib	Imaging PSA_{50} CTC	24/30	7/19	5/20	8/27	N/A
TRITON2, Abida et al. [41••]	Rucaparib	Imaging	11/25	0/5	0/8	2/8	N/A
		PSA_{50}	23/45	0/18	1/13	2/9	N/A
NCI study (50) Karzai et al. [45]	Durvalumab + olaparib	Imaging PSA_{50}	7/11	N/A	N/A	N/A	2/6
GALAHAD, Smith et al. [46]	Niraparib	Imaging PSA_{50} CTC	18/29	N/A	N/A	5/21	N/A
KEYNOTE-365, Yu et al. [47] 2019	Olaparib + pembrolizumab	Imaging	N/A	N/A	N/A	N/A	8/28
		PSA_{50}	N/A	N/A	N/A	N/A	5/41
Retrospective analysis, Marshall et al. [48]	Off-label olaparib	PSA_{50}	13/17	0/6	N/A	N/A	N/A

Mut, mutations; *CTC*, circulating tumor cell DNA; *PSA_{50}*, decline of prostate-specific antigen by 50% from baseline; *Imaging*, radiographic response measured by RECIST criteria; *rPFS*, radiographic progression-free survival

cancer is being evaluated in several ongoing clinical trials (www.clinicaltrials.gov, NCT03570476, NCT02324998 and NCT03432897).

Biochemical Recurrence

Patients historically classified as having biochemically recurrent (BCR) prostate cancer are now moved to the metastatic group with the use of more sensitive treatment modalities such as PSMA-PET and fluciclovine PET. Advances in imaging has changed the BCR patient population. There is currently no standard of care treatment implications of DNA repair mutations in BCR group, but the use of PARPi is currently being studied in phase 2 clinical trial (NCT03047135), evaluated PSA_{50} response to olaparib in BCR prostate cancer patients. The study is enrolling patients unselected for DNA repair mutation status with an adaptive plan to enrich study population with DNA repair mutation carriers if response is low in first 20 patients.

Conclusions

There has been significant advancement in prostate cancer genetics in the last 5 years. In metastatic castration-resistant prostate cancer, ~20% of tumors harbor homologous recombination repair gene mutations, and 5% harbor mismatch repair gene mutations; alternations in both pathways have clinical implications. The NCCN Prostate Cancer guidelines recommend germline testing for men with high-risk, very high-risk localized prostate cancer, all metastatic prostate cancer patients, patients with intraductal histology of prostate cancer, and for patients meeting family history criteria. Somatic tumor testing should also be considered for advanced disease as it may inform treatment decisions.

Patients with homologous recombination-deficient prostate cancer appear to respond to PARPi and platinum chemotherapy, although more individual gene-specific data is needed. The PROFound study, a phase 3 randomized clinical trial of olaparib in mCPRC patients with *BRCA1/2* and *ATM* mutations showed improved rPFS. Patients with MSI-H/MMRd are eligible for immune checkpoint inhibitor therapy in second-line treatment for mCRPC. Both germline and somatic tumor genetic testing are recommended for prostate cancer patients in specific clinical scenarios. Clinical trials are ongoing to evaluate treatment implications of alterations in mismatch repair genes and homologous recombination genes, and we expect new indications and combinations of PARPi and immune checkpoint inhibitors to be explored by these trials. Further investigation is needed to identify individual gene contributions to treatment response prediction and germline risk of prostate and other cancers.

Funding information NCI award numbers T32CA009515, P30 CA015704, P50 CA097186-16A1 (PNW Prostate SPORE), Institute for Prostate Cancer Research, Prostate Cancer Foundation

Compliance with Ethical Standards

Conflict of Interest Alexandra O. Sokolova declares that she has no conflict of interest.

Heather H. Cheng has received research funding to her institution from Inovio, Clovis Oncology, Color Genomics, Medivation, Sanofi, Astellas, Janssen.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Gudmundsson J, Sulem P, Gudbjartsson DF, Masson G, Agnarsson BA, Benediktsdottir KR, et al. A study based on whole-genome sequencing yields a rare variant at 8q24 associated with prostate cancer. Nat Genet. 2012 Dec;44(12):1326–9.
2. Amin Al Olama A, Kote-Jarai Z, Schumacher FR, Wiklund F, Berndt SI, Benlloch S, et al. A meta-analysis of genome-wide association studies to identify prostate cancer susceptibility loci associated with aggressive and non-aggressive disease. Hum Mol Genet. 2013 Jan 15;22(2):408–15.
3. Bajrami I, Frankum JR, Konde A, Miller RE, Rehman FL, Brough R, et al. Genome-wide profiling of genetic synthetic lethality identifies CDK12 as a novel determinant of PARP1/2 inhibitor sensitivity. Cancer Res. 2014 Jan 1;74(1):287–97.
4. Gudmundsson J, Sulem P, Gudbjartsson DF, Blondal T, Gylfason A, Agnarsson BA, et al. Genome-wide association and replication studies identify four variants associated with prostate cancer susceptibility. Nat Genet. 2009 Oct;41(10):1122–6.
5. Akamatsu S, Takata R, Haiman CA, Takahashi A, Inoue T, Kubo M, et al. Common variants at 11q12, 10q26 and 3p11.2 are associated with prostate cancer susceptibility in Japanese. Nat Genet. 2012 Feb 26;44(4):426–9 **S1**.
6. Goh CL, Schumacher FR, Easton D, Muir K, Henderson B, Kote-Jarai Z, et al. Genetic variants associated with predisposition to prostate cancer and potential clinical implications. J Intern Med. 2012 Apr;271(4):353–65.
7. Eeles RA, Olama AAA, Benlloch S, Saunders EJ, Leongamornlert DA, Tymrakiewicz M, et al. Identification of 23 new prostate cancer susceptibility loci using the iCOGS custom genotyping array. Nat Genet [Internet]. 2013 Apr [cited 2019 Aug 13];45(4). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3832790/
8. Ewing CM, Ray AM, Lange EM, Zuhlke KA, Robbins CM, Tembe WD, et al. Germline mutations in HOXB13 and prostate-cancer risk. N Engl J Med. 2012 Jan 12;366(2):141–9.
9. Kote-Jarai Z, Leongamornlert D, Saunders E, Tymrakiewicz M, Castro E, Mahmud N, et al. BRCA2 is a moderate penetrance gene contributing to young-onset prostate cancer: implications for genetic testing in prostate cancer patients. Br J Cancer. 2011 Oct 11;105(8):1230–4.
10. Gallagher DJ, Gaudet MM, Pal P, Kirchhoff T, Balistreri L, Vora K, et al. Germline BRCA mutations denote a clinicopathologic subset of prostate cancer. Clin Cancer Res. 2010 Apr 1;16(7):2115–21.
11. Robinson D, Van Allen EM, Wu Y-M, Schultz N, Lonigro RJ, Mosquera J-M, et al. Integrative clinical genomics of advanced prostate cancer. Cell. 2015 May 21;161(5):1215–28.
12. •• Pritchard CC, Mateo J, Walsh MF, De Sarkar N, Abida W, Beltran H, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. New England Journal of Medicine. 2016 Aug 4;375(5):443–53. **This study assesses prevalence of germline DNA repair mutations and shows prevalence of 11.8% among mCPRC patients. This study lead to NCCN recommendation of germline testing in metastatic prostate cancer.**
13. Nicolosi P, Ledet E, Yang S, Michalski S, Freschi B, O'Leary E, et al. Prevalence of germline variants in prostate cancer and implications for current genetic testing guidelines. JAMA Oncol. 2019 Apr 1;5(4):523–8.
14. Chua MLK, Lo W, Pintilie M, Murgic J, Lalonde E, Bhandari V, et al. A prostate cancer "Nimbosus": genomic instability and SChLAP1 dysregulation underpin aggression of intraductal and cribriform subpathologies. Eur Urol. 2017;72(5):665–74.
15. Böttcher R, Kweldam CF, Livingstone J, Lalonde E, Yamaguchi TN, Huang V, et al. Cribriform and intraductal prostate cancer are associated with increased genomic instability and distinct genomic alterations. BMC Cancer. 2018 02;18(1):8.
16. Seipel AH, Whitington T, Delahunt B, Samaratunga H, Mayrhofer M, Wiklund P, et al. Genetic profile of ductal adenocarcinoma of the prostate. Hum Pathol. 2017;69:1–7.
17. Schweizer MT, Antonarakis ES, Bismar TA, Guedes LB, Cheng HH, Tretiakova MS, et al. Genomic characterization of prostatic ductal adenocarcinoma identifies a high prevalence of DNA repair gene mutations. JCO Precision Oncology. 2019 Apr 18;3:1–9.
18. Taylor RA, Fraser M, Livingstone J, Espiritu SMG, Thorne H, Huang V, et al. Germline BRCA2 mutations drive prostate cancers with distinct evolutionary trajectories. Nat Commun. 2017 Jan 9;8(1):1–10.
19. Risbridger GP, Taylor RA, Clouston D, Sliwinski A, Thorne H, Hunter S, et al. Patient-derived xenografts reveal that intraductal carcinoma of the prostate is a prominent pathology in BRCA2 mutation carriers with prostate cancer and correlates with poor prognosis. Eur Urol. 2015 Mar;67(3):496–503.
20. Isaacsson Velho P, Silberstein JL, Markowski MC, Luo J, Lotan TL, Isaacs WB, et al. Intraductal/ductal histology and lymphovascular invasion are associated with germline DNA-repair gene mutations in prostate cancer. Prostate. 2018;78(5):401–7.
21. Cheng HH, Sokolova AO, Schaeffer EM, Small EJ, Higano CS. Germline and somatic mutations in Prostate Cancer for the clinician. J Natl Compr Cancer Netw. 2019 May 1;17(5):515–21.
22. Prostate Cancer NCCN Guidlines Version 4.2019 10/05/2019.
23. Genetic/Familial High-Risk Assessment: Breast and Ovarian NCCN Guidlines Version 3.2019 10/05/2019.
24. Breast Cancer Linkage Consortium. Cancer risks in BRCA2 mutation carriers. J Natl Cancer Inst. 1999 Aug 4;91(15):1310–6.
25. Leongamornlert D, Mahmud N, Tymrakiewicz M, Saunders E, Dadaev T, Castro E, et al. Germline BRCA1 mutations increase prostate cancer risk. Br J Cancer. 2012 May 8;106(10):1697–701.
26. Page EC, Bancroft EK, Brook MN, Assel M, Hassan Al Battat M, Thomas S, et al. Interim results from the IMPACT study: evidence for prostate-specific antigen screening in BRCA2 mutation carriers. Eur Urol 2019 Sep 16;
27. Eeles RA, Bancroft E, Page E, Castro E, Taylor N. Identification of men with a genetic predisposition to prostate cancer: targeted screening in men at higher genetic risk and controls—the IMPACT study. JCO. 2013 Feb 20;31(6_suppl):12–12.
28. Castro E, Goh C, Olmos D, Saunders E, Leongamornlert D, Tymrakiewicz M, et al. Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. J Clin Oncol. 2013 May 10;31(14):1748–57.
29. Castro E, Goh C, Leongamornlert D, Saunders E, Tymrakiewicz M, Dadaev T, et al. Effect of BRCA mutations on metastatic relapse and cause-specific survival after radical treatment for localised prostate cancer. Eur Urol. 2015 Aug 1;68(2):186–93.
30. • Na R, Zheng SL, Han M, Yu H, Jiang D, Shah S, et al. Germline mutations in ATM and BRCA1/2 distinguish risk for lethal and indolent prostate cancer and are associated with early age at death.

Eur Urol. 2017;71(5):740–7. **This is a retrospective case study that showed higher rate of germline *BRCA1/2* and *ATM* mutations in men who died from prostate cancer compared to men with localized disease.**

31.•• Castro E, Romero-Laorden N, Del Pozo A, Lozano R, Medina A, Puente J, et al. PROREPAIR-B: A prospective cohort study of the impact of germline DNA repair mutations on the outcomes of patients with metastatic castration-resistant prostate cancer. J Clin Oncol. 2019 Feb 20;37(6):490–503. **This is a prospective study that showed mCRPC patients with germline BRCA2 mutations had worse cancer specific survival.**

32. Marshall CH, Fu W, Wang H, Baras AS, Lotan TL, Antonarakis ES. Prevalence of DNA repair gene mutations in localized prostate cancer according to clinical and pathologic features: association of Gleason score and tumor stage. Prostate Cancer Prostatic Dis. 2018 Aug;31:1.

33. Administration USFaD. FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication. In. 2017.

34. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med. 2015 Jun 25;372(26):2509–20.

35.• Abida W, Cheng ML, Armenia J, Middha S, Autio KA, Vargas HA, et al. Analysis of the prevalence of microsatellite instability in prostate cancer and response to immune checkpoint blockade. JAMA Oncol. 2019 Apr 1;5(4):471–8. **This study evaluates prevalence of MSI/dMMR in prostate cancer and showed that 5% of mCRPC tumors have MSI/dMMR.**

36. Rescigno P, Rodrigues DN, Yuan W, Carreira S, Lambros M, Seed G, et al. Abstract 4679: mismatch repair defects in lethal prostate cancer. Cancer Res. 2017 Jul 1;77(13 Supplement):4679–9.

37. Pritchard CC, Morrissey C, Kumar A, Zhang X, Smith C, Coleman I, et al. Complex MSH2 and MSH6 mutations in hypermutated microsatellite unstable advanced prostate cancer. Nat Commun. 2014 Sep 25;5:4988.

38. Guedes LB, Antonarakis ES, Schweizer MT, Mirkheshti N, Almutairi F, Park JC, et al. MSH2 loss in primary prostate cancer. Clin Cancer Res. 2017 Nov 15;23(22):6863–74.

39. Athie A, Arce-Gallego S, Gonzalez M, Morales-Barrera R, Suarez C, Casals Galobart T, et al. Targeting DNA repair defects for precision medicine in prostate cancer. Curr Oncol Rep. 2019 Mar 27;21(5):42.

40. Mateo J, Carreira S, Sandhu S, Miranda S, Mossop H, Perez-Lopez R, et al. DNA-repair defects and olaparib in metastatic prostate cancer. N Engl J Med. 2015 Oct 29;373(18):1697–708.

41.•• Abida W., et al. Preliminary results from TRITON2: a phase 2 study of rucaparib in patients with metastatic castration-resistant prostate cancer (mCRPC) associated with homologous recombination repair (HRR) gene alterations" (abstract 793PD), ESMO 2018. **Preliminary results of a phase II trial evaluating rucaparib in patients with mCRPC and alterations in DNA repair genes.**

42. Clovis Oncology Receives Breakthrough Therapy Designation for Rubraca® (rucaparib) for Treatment of BRCA1/2-Mutated Metastatic Castration Resistant Prostate Cancer (mCRPC) [Internet]. 2018 [cited 2018 Dec 6]. Available from: https://www.businesswire.com/news/home/20181002005512/en/Clovis-Oncology-Receives-Breakthrough-Therapy-Designation-Rubraca%C2%AE

43.•• Mateo J, Porta N, McGovern UB, Elliott T, Jones RJ, Syndikus I, et al. TOPARP-B: a phase II randomized trial of the poly(ADP)-ribose polymerase (PARP) inhibitor olaparib for metastatic castration resistant prostate cancers (mCRPC) with DNA damage repair (DDR) alterations. JCO. 2019 May 20;37(15_suppl):5005–5005. **Preliminary results of a phase II study evaluating olaparib (300 mg BID and 400 mg BID) in mCRPC patients with DDR.**

44.•• Olaparib Outperforms Enzalutamide or Abiraterone Acetate | ESMO [Internet]. [cited 2019 Oct 1]. Available from: https://www.esmo.org/Oncology-News/Olaparib-Outperforms-Enzalutamide-or-Abiraterone-Acetate-in-Men-with-mCRPC-and-HRR-Alterations. **This is first phase III randomized clinical trial evaluating olaparib vs abiraterone/enzalutamide in mCRPC, that showed statistically significant improvement rPFS with olaparib in patients with BRCA1/2 and ATM mutations.**

45. Karzai F, et al. A phase 2 study of olaparib and durvalumab in metastatic castrate-resistant prostate cancer (mCRPC) in an unselected population. J Clin Oncol. 2018;36(suppl 6S; abstr 163):163

46. Smith MR, Sandhu SK, Kelly WK, et al: Phase II study of niraparib in patients with metastatic castration-resistant prostate cancer and biallelic DNA-repair defects: preliminary results of GALAHAD. 2019 Genitourinary Cancers Symposium. Abstract 202. Presented February 14, 2019.

47. Yu EY, Massard C, Retz M, et al: KEYNOTE-365 cohort A: pembrolizumab plus olaparib in docetaxel-pretreated patients with metastatic castration-resistant prostate cancer. 2019 Genitourinary Cancers Symposium. Abstract 145. Presented February 14, 2019.

48. Marshall CH, Sokolova AO, McNatty AL, Cheng HH, Eisenberger MA, Bryce AH, et al. Differential response to olaparib treatment among men with metastatic castration-resistant prostate cancer harboring BRCA1 or BRCA2 versus ATM mutations. Eur Urol. 2019 Feb;21.

49. Alsop K, Fereday S, Meldrum C, deFazio a, Emmanuel C, George J, et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. J Clin Oncol 2012 Jul 20;30(21):2654–2663.

50. Chetrit A, Hirsh-Yechezkel G, Ben-David Y, Lubin F, Friedman E, Sadetzki S. Effect of BRCA1/2 mutations on long-term survival of patients with invasive ovarian cancer: the national Israeli study of ovarian cancer. J Clin Oncol. 2008 Jan 1;26(1):20–5.

51. Cheng HH, Pritchard CC, Boyd T, Nelson PS, Montgomery B. Biallelic inactivation of BRCA2 in platinum sensitive, metastatic castration resistant prostate cancer. Eur Urol. 2016 Jun;69(6):992–5.

52. Pomerantz MM, Spisák S, Jia L, Cronin AM, Csabai I, Ledet E, et al. The association between germline BRCA2 variants and sensitivity to platinum-based chemotherapy among men with metastatic prostate cancer. Cancer. 2017 Sep 15;123(18):3532–9.

53. Carter HB, Helfand B, Mamawala M, Wu Y, Landis P, Yu H, et al. Germline mutations in ATM and BRCA1/2 are associated with grade reclassification in men on active surveillance for prostate cancer. Eur Urol. 2018 Oct;8.

Published OnlineFirst March 31, 2020; DOI: 10.1158/1078-0432.CCR-20-0707

Honing in on PARPi Response in Prostate Cancer: from HR Pathway to Gene-by-Gene Granularity

Alexandra O. Sokolova[1,2,3], Evan Y. Yu[1,2], and Heather H. Cheng[1,2]

SUMMARY

PARP inhibitors (PARPi) are promising in *BRCA2*-altered prostate cancer. Data were presented on PARPi efficacy in prostate cancers with alterations in other DNA damage repair genes which suggest low response rates in *ATM*-, *CHEK2*-, *CDK12*-altered tumors and promising results in *PALB2*-, *RAD51B*-, *FANCA*-, and *BRIP1*-altered tumors.

See related article by Abida et al., p. 2487

In this issue of *Clinical Cancer Research*, Abida and colleagues report response to the PARPi rucaparib in patients with metastatic castration resistant prostate cancer (mCRPC) harboring deleterious alterations in non-*BRCA* DNA damage repair (DDR) genes (1). The data provides early evidence that prostate tumors with *ATM, CDK12*, and *CHEK2* alterations may have limited response to rucaparib, while tumors with alterations in *PALB2, FANCA, BRIP1*, and *RAD51B* may benefit from PARP inhibition (1).

Several studies suggest that PARPis are effective in prostate cancer tumors with *BRCA2* alterations (2). The mechanism of action of PARPi in tumors is typically attributed to impaired double-strand DDR-homologous recombination (HR) repair–deficient tumors, but likely involves additional mechanisms such as (i) trapping of the PARP1–enzyme, which regulates several DNA repair processes; (ii) inhibition of base excision, critical to single-strand DNA repair; (iii) activation of error prone nonhomologous end joining repair, important in double-strand DNA repair; and (iv) inhibition of DNA repair protein recruitment (e.g., *BARD1-BRCA1* complex; ref. 3). Multiple non-*BRCA* genes mediate HR repair (*e.g., ATM, CHEK2*, and others), so many have been included as candidate biomarkers for PARPi sensitivity. However, data to date has been limited by small numbers and technical differences (2).

To begin to address this, Abida and colleagues evaluated response to rucaparib in patients with metastatic castration-resistant prostate cancer and non-*BRCA* DDR gene alterations in the phase II TRITON2 study. Eligibility included patients with disease progression after second-generation androgen receptor–targeted therapy and taxane-based chemotherapy and who were identified to have germline and/or somatic mutations in selected DDR genes (*BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK2, FANCA, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D*, or *RAD54L*). Whole blood was used for germline testing and somatic sequencing was performed on circulating tumor DNA (ctDNA) or on tumor tissue by central or local laboratory. This *ad hoc* analysis included 78 patients whose tumors were found to have alterations in non-*BRCA* DDR genes. Response was defined as partial or complete radiographic response per RECIST criteria or PSA50 response (decline of serum prostate-specific antigen by 50% from baseline). Overall rates of response among patients with *ATM, CHEK2*, and *CDK12* alterations were low: 2/49 (*ATM*), 2/12 (*CHEK2*), 1/15 (*CDK12*). Interestingly, the proportion of patients without evidence of radiographic progression (labeled clinical benefit) at 6 and 12 months suggests that rucaparib may stabilize disease in these patients. Responses were observed in 2 of 2 patients with *PALB2*, 1/4 with *FANCA*, 1/2 with *BRIP1*, 1/1 with *RAD51B* mutations, small, but intriguing numbers.

These findings are consistent with previously reported data: 1 of 5 patients with *FANCA*-, 4/7 with *PALB2*-, 2/19 with *ATM*-, and 0/20 with *CDK12* -alterations had RECIST or PSA50 response to PARPi in TOPARP-B trial (2). In the PROfound study, patients with *RAD51B* alterations treated with PARPi had a 6-month median radiographic progression-free survival (rPFS) benefit compared with physician choice therapy arm, and similar rPFS was observed between two arms in patients with *ATM* alterations (2). Similarly 0 of 6 patients with *ATM* alterations had PSA50 response in a retrospective study (2). As a field, we must be careful to draw conclusions from small numbers in each analysis, however, in aggregate, patterns are emerging.

The authors of this manuscript acknowledge several limitations (1). First, there was no requirement for central laboratory confirmation of reported alterations. Some, but not all, sequencing results were confirmed by central laboratory, increasing the chance of false positive results for eligibility. Second, clonal hematopoietic (CH) variants may introduce interference in ctDNA studies and mistakenly attributed to tumor-specific alterations (4). Among genes included for eligibility in this study, alterations in *ATM* are more common in CH and thus may contribute to variant origin misclassification (4). Third, loss of heterozygosity (LOH) and tumor sequencing data were not available for several patients, including the patients with *ATM* alterations who had response to rucaparib. It is possible that non-*ATM* tumor alterations contributed to PARPi responses in these patients even though their eligibility was due to an *ATM* alteration.

This study addresses important knowledge gaps by characterizing response to PARPi in tumors with relatively rare alterations in DDR genes. It is especially timely as we anticipate FDA approval of PARPi in prostate cancer based on the positive phase III PROfound study and other eagerly anticipated trials such as TRITON3, GALAHAD and TALAPRO-1 (2). Understanding the efficacy of PARPi in prostate tumors with non-*BRCA* DDR gene alterations is essential before

[1]Department of Medicine, University of Washington, Seattle, Washington. [2]Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington. [3]VA Puget Sound Health Care System, Tacoma, Washington.

Corresponding Author: Heather H. Cheng, University of Washington, 825 Eastlake Ave E, Seattle, WA 98109. Phone: 206-606-1943; Fax: 206-606-2042; E-mail: hhcheng@uw.edu

Clin Cancer Res 2020;26:2439–40

doi: 10.1158/1078-0432.CCR-20-0707

Published OnlineFirst March 31, 2020; DOI: 10.1158/1078-0432.CCR-20-0707

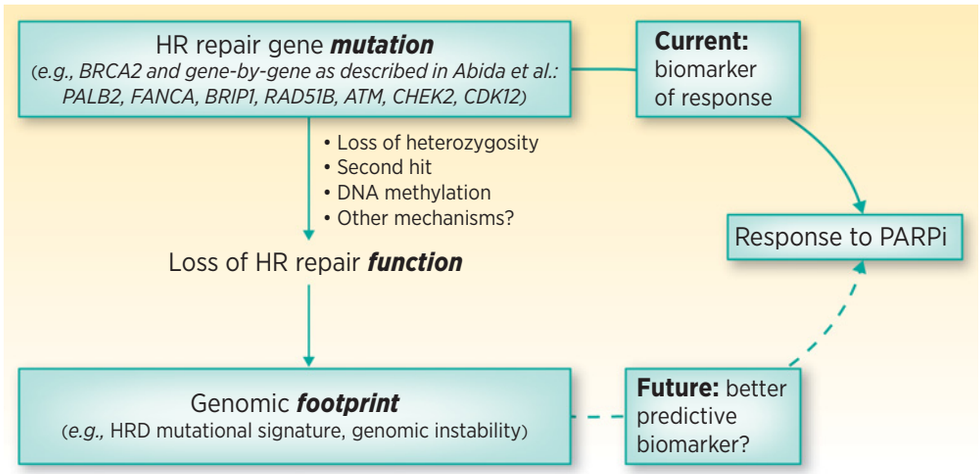


Figure 1.

Predictive biomarkers for PARPi efficacy. Currently, alterations in HR repair genes are used to predict loss of HR repair function and to select prostate cancer patients most likely to respond to PARPi, potentially overlooking other causes of HR function loss. HR repair function loss consequences (i.e., genomic footprint) may be a better predictive biomarker for response to PARPi. HRD, homologous recombination deficiency.

widespread clinical use makes the task more challenging. The data presented by Abida and colleagues may help generate hypotheses about mechanisms of response and resistance, and refine predictive biomarkers for PARPi use for patients with prostate cancer, including in subsequent preclinical and clinical trials.

A better understanding of which patients benefit the most from PARPi and which DDR gene mutations could be the best predictors of response to PARPi will help refine precision oncology in prostate cancer therapy. A notable example is that not all *BRCA2*-mutated tumors respond to PARPi (1, 2) and conversely, in the TOPARP-A study, two patients without evidence of DDR gene mutations achieved response to PARPi, suggesting additional mechanisms of PARPi sensitivity beyond those specifically tested (2). Sensitivity to PARPi is hypothesized to be determined by functional HR deficiency (HRD), such that relying solely on gene mutations to predict PARPi sensitivity may overlook other mechanisms resulting in loss of HR function, for example, DNA hypermethylation. Loss of HR repair function, regardless of the cause, is thought to lead to characteristic genomic changes such as HRD mutational signature and genomic instability. HRD mutational signature is characterized by a more-or-less equal representation of all possible single base substitutions and all 96 mutant nucleotide contexts (5). With the data and specimens from Abida and colleagues and other PARPi studies, examining the downstream consequences of HR loss and the associated genomic footprints with clinical response may facilitate more accurate prediction of response to PARPi in the future (**Fig. 1**).

We applaud the authors in reporting their findings of response to PARPi in tumors with non-*BRCA* DDR gene alterations. To further strengthen the available data for patients whose tumors carry these and other rare alterations and the response to PARPi and other treatments, a concerted team approach is needed. Assembling greater numbers of patients with rare mutations will allow more robust investigation of clinical response, mutational signatures of specific gene alterations, mechanisms of resistance such as reversion mutations, and opportunities for model systems to dissect mechanisms. This will further refine predictive biomarkers, stratify appropriate patients to PARPi therapy and improve the precision of our targeted therapies.

Disclosure of Potential Conflicts of Interest

E.Y. Yu is a paid consultant for AstraZeneca, Clovis, Merck, and Janssen, and reports receiving commercial research grants from Merck. H.H. Cheng is a paid consultant for AstraZeneca and reports receiving other commercial research support from Clovis Oncology, Janssen, Medivation, Sanofi, and Color Genomics. No potential conflicts of interest were disclosed by the other author.

Acknowledgments

We gratefully acknowledge funding support from the Prostate Cancer Foundation (to H. H. Cheng), National Cancer Institute [T32CA009515, to A.O. Sokolova; P50 CA097186-16A1 (PNW Prostate SPORE), to H.H. Cheng and E. Y. Yu; and P30 CA015704, to H.H. Cheng and E.Y. Yu], and Brotman Baty Institute (to H.H. Cheng).

Received March 12, 2020; revised March 20, 2020; accepted March 27, 2020; published first March 31, 2020.

References

1. Abida W, Campbell D, Patnaik A, Shapiro JD, Sautois B, Vogelzang NJ, et al. Non-BRCA DNA damage repair gene alterations and response to the PARP inhibitor rucaparib in metastatic castration-resistant prostate cancer: Analysis From the Phase II TRITON2 Study. Clin Cancer Res 2020;26:2487–96.
2. Sokolova AO, Cheng HH. Genetic testing in prostate cancer. Curr Oncol Rep 2020;22;5.
3. Scott CL, Swisher EM, Kaufmann SH. Poly (ADP-ribose) polymerase inhibitors: recent advances and future development. J Clin Oncol 2015;33:1397–1406.
4. Ptashkin RN, Mandelker DL, Coombs CC, Bolton K, Yelskaya Z, Hyman DM, et al. Prevalence of clonal hematopoiesis mutations in tumor-only clinical genomic profiling of solid tumors. JAMA Oncol 2018;4:1589–93.
5. Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SAJR, Behjati S, Biankin AV, et al. Signatures of mutational processes in human cancer. Nature 2013;500:415–21.

Published OnlineFirst March 31, 2020; DOI: 10.1158/1078-0432.CCR-20-0707

AACR American Association for Cancer Research

Clinical Cancer Research

Honing in on PARPi Response in Prostate Cancer: from HR Pathway to Gene-by-Gene Granularity

Alexandra O. Sokolova, Evan Y. Yu and Heather H. Cheng

Clin Cancer Res 2020;26:2439-2440. Published OnlineFirst March 31, 2020.

Two Steps Forward and One Step Back for Precision in Prostate Cancer Treatment

Michael T. Schweizer, MD[1,2]; Heather H. Cheng, MD, PhD[1,2]; Peter S. Nelson, MD[1,2,3]; and R. Bruce Montgomery, MD[1,2,4]

The recent US Food and Drug Administration approval of two poly (ADP-ribose) polymerase (PARP) inhibitors, rucaparib and olaparib, for men with metastatic castration-resistant prostate cancer (mCRPC) and mutations in homologous recombination (HR) repair genes has finally ushered in the era of precision medicine for advanced prostate cancer.[1-4] These approvals represent the culmination of years of work and are clearly a major step forward for the field. However, the respective labels for rucaparib and olaparib offer stark contrasts, the former restrictive to only *BRCA1*- and *BRCA2*-mutated prostate cancer, and the latter permissive of a larger number of genes directly and indirectly involved in HR repair. The broad approval for olaparib includes several genes that, to date, have not individually been shown to predict for response to PARP inhibition. The unintended consequence of using this permissive biomarker strategy for selecting patients for PARP inhibitor treatment may be that patients who have an unclear chance of benefit are exposed to toxicities and delays in utilizing more effective therapies. In addition, this broad approval could hamper efforts to enroll patients in studies designed to better delineate the ability of relatively rare mutations to predict response to PARP inhibitors.

Rucaparib was granted accelerated approval on the basis of the phase II TRITON2 study.[1,3] In this trial, patients with mCRPC were eligible if they previously experienced progression on a next-generation androgen receptor–signaling inhibitor (eg, abiraterone, enzalutamide, or apalutamide), received one prior line of taxane-based chemotherapy, and who were identified to have a mutation in at least one gene of a larger panel with roles in HR DNA repair. However, only the group consisting of those with *BRCA1* or *BRCA2* mutations clearly seemed to be predictive of response.[5] In total, 115 patients with *BRCA*-mutated mCRPC enrolled, with 62 having measurable disease. Within this group, a confirmed objective radiographic response was observed in 27 patients (44%), with a duration of response 6 months or longer in 56% of responders (range, 1.7 to ≥ 24 months).[1]

Whereas the final TRITON2 results are still anticipated, results of a subgroup analysis evaluating clinical outcomes in those with non–*BRCA*-mutated mCRPC enrolled has recently been reported.[5] Overall, responses in those with *ATM* (n = 49), *CDK12* (n = 15), *CHEK2* (n = 12), or other HR genes (n = 14) were low. The prostrate-specific antigen (PSA) response rate (ie, 50% or greater decline in PSA) was observed in only 4% of *ATM*-mutated cases, 7% of *CDK12*-mutated cases, and 17% of *CHEK2*-mutated cases. Radiographic responses in the subset with measurable disease were similarly low in non-*BRCA* HR repair genes. Small numbers of patients with mutations in *FANCA* (n = 4), *NBN* (n = 4), *BRIP1* (n = 2), *PALB2* (n = 2), *RAD51* (n = 1), *RAD51B* (n = 1), and/or *RAD54L* (n = 1) were also reported. Whereas sample size limitations prevent drawing conclusions about the sensitivity of any given gene, it is notable that responses were observed in those with mutations in genes that directly interact with the BRCA complex (ie, *PALB2*, *FANCA*, and *BRIP1*), which contrasts with the low response rates in genes that either sense DNA damage (eg, *ATM*, *CHEK2*) or indirectly regulate *BRCA* expression (eg, *CDK12*). Finally, it is worth acknowledging that relatively few men with *BRCA1* alterations were included in this study (n = 14), and the true response rate within this population also remains poorly defined.[6]

Olaparib was approved on the basis of the phase III PROfound study, which was a randomized, open-label study evaluating olaparib versus physician's choice of enzalutamide or abiraterone in men with mCRPC and deleterious germline or somatic mutations in HR repair genes.[4] Similar to TRITON2, the PROfound investigators also focused on the subgroup that previously experienced progression on next-generation androgen receptor–directed therapy, and, also similar to TRITON2, enrollment was allowed on the basis of a panel of genes involved in the HR repair pathway. Primary end point was progression-free survival (PFS) in the group with *BRCA1*, *BRCA2*, and/or *ATM* mutations (cohort A). A second cohort consisted of patients with mutations in other HR repair–associated genes (cohort B). Secondary end points were analyzed in a hierarchical fashion to control for trial-wide Type 1 error associated with multiple testing, which occurred in the following order: objective response rate (cohort A),

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on July 30, 2020 and published at ascopubs.org/journal/jco on September 8, 2020: DOI https://doi.org/10.1200/JCO.20.01755

PFS (combined cohorts A and B), time to pain progression (cohort A), and overall survival (cohort A).

The primary end point was met, with a PFS of 7.4 months versus 3.6 months ($P < .001$) in the olaparib versus control groups for cohort A. Secondary end points also favored the olaparib group, with an objective response rate in cohort A of 33% versus 2% in control group ($P < .001$), median PFS of 5.8 months versus 3.5 months for combined cohorts A and B ($P < .001$), median overall survival of 18.5 months versus 15.1 months for cohort A ($P = .02$), and median overall survival of 17.5 months versus 14.3 months for combined cohorts A and B ($P = .0063$). These results led the US Food and Drug Administration to approve olaparib for a broad group of patients with mCRPC with somatic or germline alterations in *BRCA1*, *BRCA2*, or any of 12 additional HR repair pathway genes.

Whereas the magnitude of benefit reported for cohort A in PROfound is apparent, the lack of details provided for cohort B leaves more questions than answers. Examining the data more closely, it seems that the observed benefit was largely driven by *BRCA*-mutated patients, which primarily consisted of men with *BRCA2* mutations (> 90%). There is a clear improvement in PFS for the *BRCA*-mutated group (n = 160), whereas no difference in PFS was observed in either *ATM* (n = 86) or *CDK12*-mutated cases (n = 89; Fig 2B and Supplemental Figure S5). Unfortunately, no detailed analysis of outcomes for cohort B—independent of cohort A—are provided, and the small sample size within any given genomic subgroup limits our ability to determine which of these patients may have benefited from olaparib.

The TOPARP-A and -B studies, which preceded PROfound, tested olaparib in a similar patient population.[7,8] In TOPARP-B, the authors found low PSA and radiographic response rates for *ATM* (5.3% and 8.3%, respectively) and *CDK12*-mutated mCRPC (0% for both).[8] In addition, the PROfound investigators acknowledged that the benefits of olaparib are most apparent in *BRCA*-mutated mCRPC. Whereas the design of PROfound was likely informed by the initial TOPARP-A experience, which found that four of five patients with *ATM*-mutatations responded favorably to olaparib (ie, PSA response and/or favorable changes in circulating tumor cell counts), the biologic and clinical rationale for combining *ATM* and *BRCA1/2* mutations into a single cohort is questionable on the basis of our current knowledge.[7] Registries capturing clinical and genomics data are ongoing and may provide important insights into the clinical relevance of rare variants[9]; however, additional prospective studies evaluating outcomes for patients with HR repair–associated mutations receiving PARP inhibitors should be conducted on an individual gene basis.

In the case of PROfound, the *BRCA* group seems to have driven the overall effect size observed between the olaparib and control groups. An important concern is that this experience may motivate the design of future precision medicine trials. The precedent set by the olaparib approval for prostate cancer may incentivize studies that combine molecular subgroups to attain broad indications. This may lead to future study designs that include two groups: one that is expected to benefit (eg, *BRCA2*) and another that is more exploratory and permissive (eg, *ATM*/*CDK12*). The consequence, intended or not, may be that a *P* value less than .05 could be reached in the combined group as long as the sample size is sufficient to detect a diluted treatment effect. This approach would ultimately run counter to the idea of precision oncology.

As discussed above, the clinical data supporting the use of PARP inhibitors in non–*BRCA2*-mutated cases remain scant; however, there is a rationale for their routine use in men with mutations in a handful of other HR repair–associated genes. Whereas some data suggest lower response rates in men with *BRCA1*- compared with *BRCA2*-mutated prostate cancer (eg, PSA response rate of 29% *v* 56% per TRITON2) and no clear difference in PFS was observed in men with *BRCA1* mutations receiving olaparib versus abiraterone/enzalutamide in PROfound, the small number of patients with *BRCA1* mutations included in prospective studies make drawing conclusions regarding differences in activity impossible.[4,6] Overall, the known biologic role of *BRCA1* in HR repair, along with available clinical data, generally supports the use of both olaparib and rucaparib in these patients. Likewise, there is also evidence that PARP inhibitors may afford benefits to those with *PALB2* mutations, with responses to olaparib documented in approximately one third of *PALB2*-mutated prostate cancers.[8] In addition, because *PALB2* also plays a critical role in HR repair—directly interacting with the BRCA complex—there is a strong biologic rationale for using PARP inhibitors in patients with prostate cancer with inactivating *PALB2* mutations.[5,8,10,11]

The primary advantage of olaparib's broad approval is that providers will have the latitude to use this drug in men with mutations in less common HR repair genes (eg, *PALB2*) that are likely predictive for response. However, approving olaparib for such a large genomic subgroup could prove detrimental to some patients and the field if not used judiciously. To qualify for olaparib, patients must have already experienced progression on a next-generation hormonal agent (eg, abiraterone or enzalutamide) and owing to the heavily pretreated state of their disease, this population often has rapid disease progression with a short overall survival. On the basis of the published studies, there are limited data to support use of olaparib in the absence of *BRCA1/2* mutations, and without other indications of HR repair deficiency, these patients would be better served by participating in clinical trials or receiving a therapy that is beneficial in unselected patients (eg, taxane-based chemotherapy).[12] Using standard-of-care PARP inhibitors in those with uncertain or little chance of

benefit could mean missing a window of opportunity for more effective therapy. This may result in decreased survival and hamper clinical trial enrollment to the very studies that could define the predictive utility of individual genes. Cumulative experience should matter, and given our understanding of which genes predict response to PARP inhibitors, the use of rucaparib and olaparib should be primarily limited to those with *BRCA1/2* mutations until the development of additional biomarkers that are more predictive of benefit.

AFFILIATIONS

[1]Division of Oncology, Department of Medicine, University of Washington, Seattle, WA
[2]Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA
[3]Division of Human Biology, Fred Hutchinson Cancer Research Center, Seattle, WA
[4]VA Puget Sound Health Care System, Seattle, WA

CORRESPONDING AUTHOR

Michael T. Schweizer, MD, University of Washington, 825 Eastlake Ave E, Seattle, WA 98109; e-mail: schweize@uw.edu.

SUPPORT

Funded by National Institutes of Health SPORE Grant No. CA097186.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.20.01755.

AUTHOR CONTRIBUTIONS

Financial support: Peter S. Nelson
Administrative support: Michael T. Schweizer
Conception and design: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

REFERENCES

1. US Food and Drug Administration: Rubraca package insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/209115s003lbl.pdf
2. US Food and Drug Administration: Lynparza package insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208558s001lbl.pdf
3. Abida W, Bryce AH, Vogelzang NJ, et al: Preliminary results from TRITON2: A phase 2 study of rucaparib in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) associated with homologous recombination repair (HRR) gene alterations. Ann Oncol 29, 2018 (suppl 8; abstr 793PD)
4. de Bono J, Mateo J, Fizazi K, et al: Olaparib for metastatic castration-resistant prostate cancer. N Engl J Med 382:2091-2102, 2020
5. Abida W, Campbell D, Patnaik A, et al: Non-BRCA DNA damage repair gene alterations and response to the PARP inhibitor rucaparib in metastatic castration-resistant prostate cancer: Analysis from the phase II TRITON2 study. Clin Cancer Res 26:2487-2496, 2020
6. Abida W, Campbell D, Patnaik A, et al: Genomic characteristics associated with clinical activity of rucaparib in patients (pts) with BRCA1 or BRCA2 (BRCA)-mutated metastatic castration-resistant prostate cancer (mCRPC). J Clin Oncol 38, 2020 (suppl; abstr 178)
7. Mateo J, Carreira S, Sandhu S, et al: DNA-repair defects and olaparib in metastatic prostate cancer. N Engl J Med 373:1697-1708, 2015
8. Mateo J, Porta N, Bianchini D, et al: Olaparib in patients with metastatic castration-resistant prostate cancer with DNA repair gene aberrations (TOPARP-B): A multicentre, open-label, randomised, phase 2 trial. Lancet Oncol 21:162-174, 2020
9. Carlo MI, Giri VN, Paller CJ, et al: Evolving intersection between inherited cancer genetics and therapeutic clinical trials in prostate cancer: A white paper from the Germline Genetics Working Group of the Prostate Cancer Clinical Trials Consortium. JCO Precis Oncol 10.1200/PO.18.00060
10. Antoniou AC, Foulkes WD, Tischkowitz M: Breast-cancer risk in families with mutations in PALB2. N Engl J Med 371:1651-1652, 2014
11. Ducy M, Sesma-Sanz L, Guitton-Sert L, et al: The tumor suppressor PALB2: Inside out. Trends Biochem Sci 44:226-240, 2019
12. de Wit R, de Bono J, Sternberg CN, et al: Cabazitaxel versus abiraterone or enzalutamide in metastatic prostate cancer. N Engl J Med 381:2506-2518, 2019

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Two Steps Forward and One Step Back for Precision in Prostate Cancer Treatment

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Michael T. Schweizer
Consulting or Advisory Role: Janssen, Resverlogix
Research Funding: Janssen (Inst), AstraZeneca (Inst), Roche (Inst), Pfizer (Inst), Zenith Epigenetics (Inst), Madison Vaccines (Inst), Immunomedics (Inst)

Heather H. Cheng
Consulting or Advisory Role: AstraZeneca (Inst)
Research Funding: Sanofi (Inst), Janssen (Inst), Clovis Oncology (Inst), Color Foundation (Inst)

Peter S. Nelson
Consulting or Advisory Role: Janssen Oncology, Astellas Pharma, Genentech, Bristol Myers Squibb
Research Funding: Genomic Health (Inst)
Expert Testimony: Veneble-Fitzpatrick Law Firm
Travel, Accommodations, Expenses: Janssen Oncology

R. Bruce Montgomery
Research Funding: AstraZeneca (Inst), Janssen Oncology (Inst), Clovis (Inst), Astellas Pharma (Inst), Beigene (Inst)

No other potential conflicts of interest were reported.

PLOS ONE

RESEARCH ARTICLE

Impact of mutations in homologous recombination repair genes on treatment outcomes for metastatic castration resistant prostate cancer

Alexander S. Carlson[1], Rigo I. Acevedo[1], Daniel M. Lim[1], Roman Gulati[2], Agnes Gawne[3], Alexandra O. Sokolova[3,4], Heather H. Cheng[3,4], Peter S. Nelson[1,3,4,5], R. Bruce Montgomery[3,4], Evan Y. Yu[3,4], Michael T. Schweizer[3,4]*

1 University of Washington, Seattle, WA, United States of America, **2** Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, United States of America, **3** Division of Oncology, University of Washington, Seattle, WA, United States of America, **4** Division of Clinical Research, Fred Hutchinson Cancer Research Center, Seattle, WA, United States of America, **5** Division of Human Biology, Fred Hutchinson Cancer Research Center, Seattle, WA, United States of America

* schweize@uw.edu

OPEN ACCESS

Citation: Carlson AS, Acevedo RI, Lim DM, Gulati R, Gawne A, Sokolova AO, et al. (2020) Impact of mutations in homologous recombination repair genes on treatment outcomes for metastatic castration resistant prostate cancer. PLoS ONE 15(9): e0239686. https://doi.org/10.1371/journal.pone.0239686

Editor: Alvaro Galli, CNR, ITALY

Received: June 26, 2020

Accepted: August 14, 2020

Published: September 30, 2020

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: We acknowledge research support from National Cancer Institute grants P30 CA015704, R50 CA221836 (RG) and P50 CA97186 (PSN); Department of Defense Awards W81XWH-18-1-0406 (PSN) and W81XWH-18-1-035 (PSN); NIH Training Award T32CA009515 (AOS); and from the Institute for Prostate Cancer Research. The funders had no role in study design, data collection and

Abstract

Introduction

A significant proportion of patients with metastatic castration-resistant prostate cancer (mCRPC) harbor mutations in homologous recombination (HR) repair genes, with some of these mutations associating with increased tumor susceptibility to poly(ADP-ribose) polymerase (PARP) inhibitors and platinum-based chemotherapy. While mutations in some HR repair genes (e.g., *BRCA1/2*) have been associated with a more aggressive clinical course, prior studies correlating HR mutational status with treatment response to androgen receptor (AR) signaling inhibitors (ARSIs) or taxane-based chemotherapy have yielded conflicting results.

Methods

We conducted a single-center retrospective analysis to assess clinical outcomes to conventional, regulatory-approved therapies in mCRPC patients with somatic (monoallelic and biallelic) and/or germline HR repair mutations compared to patients without alterations as determined by clinical-grade next-generation sequencing assays. The primary endpoint was PSA30/PSA50 response, defined as $\geq$30%/$\geq$50% prostate-specific antigen (PSA) reduction from baseline. Secondary endpoints of PSA progression-free survival (pPFS) and clinical/radiographic progression-free survival (crPFS) were estimated using Kaplan-Meier methods.

Results

A total of 90 consecutively selected patients were included in this analysis, of which 33 (37%) were identified to have HR repair gene mutations. Age, race, Gleason score, prior

analysis, decision to publish, or preparation of the manuscript.

Competing interests: HHC has served as a paid consultant to AstraZeneca and received research funding to her institution from Clovis Oncology, Janssen, Medivation, Sanofi Aventis and Color Genomics. PSN has served as a paid consultant to Janssen, Astellas and Bristol Myers Squibb. RBM has received research funding to his institution from Clovis, Janssen, Astellas, Beigene and AstraZeneca. EYY has served as a paid consultant and/or received an honorarium from Abbvie, Advanced Accelerator Applications, Amgen, Astrazeneca, Bayer, Churchill, Clovis, Dendreon, EMD Serono, Genentech, Incyte, Janssen, Lilly, Merck, Pharmacyclics, QED, Sanofi-Genzyme, Seattle Genetics, Tolmar and has received research funding to his institution from Bayer, Daiichi-Sankyo, Dendreon, Genentech, Merck, Pharmacyclics, Seattle Genetics and Taiho. MTS has served as a paid consultant to Janssen and Resverlogix. He has received research funding to his institution from Immunomedics, Janssen, AstraZeneca, Pfizer, Madison Vaccines, Tmunity and Hoffman-La Roche. All other authors have no competing interests to disclose. This does not alter our adherence to PLOS ONE policies on sharing data and materials. There are no patents, products in development or marketed products to declare.

surgery, and receipt of prior radiation therapy were comparable between carriers and non-carriers. There was no evidence that PSA30/PSA50 differed by HR gene mutational status. Median pPFS and crPFS ranged 3–14 months across treatment modalities, but there was no evidence either differed by HR gene mutational status (all p>0.05). There was also no difference in outcomes between those with *BRCA2* or *PALB2* mutations (n = 17) compared to those without HR repair mutations.

Conclusion

HR gene mutational status was associated with comparable clinical outcomes following treatment with ARSIs or taxane-based chemotherapy. Additional prospective studies are needed to confirm these findings.

Introduction

DNA damage repair (DDR) pathways play an essential role in maintaining genomic integrity. Individuals harboring germline mutations in DDR genes are more susceptible to cancer development [1]. Germline and somatic DDR mutations are also associated with a more aggressive clinical course in certain cancers: germline *BRCA* mutations have been associated with decreased breast cancer-specific survival [2] and linked to poor outcomes in patients with prostate cancer, including decreased metastasis-free survival in those initially presenting with localized disease [3, 4]. The significance of DDR mutations in prostate cancer has expanded in recent years as studies have demonstrated that their prevalence is higher than previously thought [5, 6].

Importantly, DDR genes specifically involved in homologous recombination (HR) repair may be predictive for response to poly(ADP-ribose) polymerase (PARP) inhibitors in patients with metastatic castration-resistant prostate cancer (mCRPC). Treatment with PARP inhibitors leads to persistent single-strand DNA (ssDNA) breaks through inhibition of base excision repair. These ssDNA breaks then degenerate to double-strand DNA (dsDNA) breaks and, because HR repair deficient cells are unable to efficiently repair dsDNA breaks, PARP inhibitors are synthetically lethal to these cancer cells [7, 8]. Various other mechanisms likely contribute to PARP inhibitor sensitivity in HR repair deficient tumors, including PARP1 trapping and creation of cytotoxic PARP1-DNA complexes at sites of endogenous damage, the promotion of nonhomologous end joining (NHEJ) activity, and inhibition of DNA repair protein recruitment (e.g., *BRCA1*, *BARD1*) [9, 10].

The two-stage TOPARP trials revealed high response rates to olaparib in mCRPC patients with HR repair gene mutations who were no longer responding to standard therapies [11, 12]. More recently, the phase III PROfound trial demonstrated increased radiographic progression-free survival (PFS) and objective responses in mCRPC patients with HR repair gene mutations receiving olaparib compared to enzalutamide or abiraterone [13], although activity in the patients with mutations in non-*BRCA*-mutated HR repair genes remains uncertain [12, 14, 15]. The phase II TRITON2 study found no clear evidence of response to rucaparib in patients with *ATM*, *CDK12*, and *CHEK2* mutations, whereas patients with mutations in genes that directly interact with the *BRCA* complex (e.g. *PALB2*, *FANCA*, *RAD51*, etc.) showed promising radiographic and prostate-specific antigen (PSA) response [15]. Rupacarib has since gained accelerated FDA approval for mCRPC patients with deleterious *BRCA1/2* mutations who were previously treated with novel androgen receptor (AR) targeted therapy and

taxane chemotherapy [16]. Olaparib has received full approval for mCRPC patients who have at least one line of novel AR targeted therapy and have a suspected or known deleterious HR repair mutation across a broad panel [17].

The presence of HR repair gene mutations in cancers has also been associated with enhanced sensitivity to platinum-based chemotherapy. The likely mechanism behind this sensitivity is through the formation of dsDNA breaks via DNA adducts [18].

Cheng, et al. reported that patients with biallelic *BRCA2* inactivation can achieve excellent clinical response with carboplatin even after progression on first-line therapies for mCRPC [19]. Germline *BRCA2* variants were also found to strongly associate with PSA response $\geq$50% in mCRPC patients treated with carboplatin [20].

While significant effort has gone into exploring precision medicine approaches for treating prostate cancer patients with HR repair gene mutations, there are limited reports describing the clinical course of these patients following treatment with standard therapies. Androgen receptor signaling inhibitors (ARSIs), such as abiraterone and enzalutamide, as well as taxane-based chemotherapy, such as docetaxel and cabazitaxel, have been established as standard, regulatory-approved treatment options for patients with mCRPC [21]. Recently, Hussain, et al. reported that somatic HR repair mutations may be associated with improved PSA response and PFS with abiraterone [22]. This contrasted with previous findings of attenuated ARSI response in germline HR gene mutation carriers [23]. Studies examining taxane-based chemotherapy treatment in mCRPC found no significant difference in treatment responses when stratifying by HR gene mutation status [24, 25]. Notably, treatment with cabazitaxel was not evaluated in these reports.

The objective of this paper is to investigate how mutations in genes directly and indirectly involved in the HR repair pathway impact treatment response and long-term outcomes in mCRPC patients treated with abiraterone, enzalutamide, docetaxel, and cabazitaxel. We hypothesized that the presence of HR repair gene mutations will correlate with poor clinical outcomes following treatment with these agents.

Materials and methods

Patients

A retrospective analysis was performed using the institutional Caisis database, which includes prostate cancer patients treated at the University of Washington/Seattle Cancer Care Alliance (UW/SCCA). Prior to data abstraction, this project was reviewed by the Institutional Review Board at the University of Washington and deemed to be minimal risk. As such, the requirement for informed consent was waived. Patient electronic medical records were accessed between 05/2018-02/2020 and were not anonymized to data abstractors. All patient data was de-identified prior to performing statistical analysis.

Our inclusion criteria mandated that patients have pathologically proven prostate cancer and documented mCRPC status, defined as disease progression following surgical/medical castration (i.e. androgen deprivation therapy; ADT) by PSA or radiographic/clinical evidence. Additionally, patients must have previously undergone clinical-grade next-generation sequencing (NGS) of their tumor. An exception was made to include patients with known germline *BRCA2* mutations who did not undergo tumor sequencing, given that these germline cases are most often associated with the loss of the second allele by somatic mutation [6]. The following assays were included: UW-OncoPlex, FoundationOne, Guardant360, GeneTrails, BROCA, Color, BRACAnalysis, and Whole Exome Sequencing (WEC) assay results [5].

We specifically analyzed monotherapy treatments with each of the four agents (abiraterone, enzalutamide, docetaxel, cabazitaxel) that occurred between 2011–2019. Per Prostate Cancer

Working Group 3 (PCWG3) guidelines, we required a minimum 60 days of therapy in order to assess responses and progression endpoints [26]. Patients treated with more than one of the four agents were eligible for analysis in multiple treatment groups if all above inclusion criteria were met. If a patient received multiple courses of the same agent, only the first treatment course was assessed. Confirmation of PSA response/progression was not required since this was not uniformly performed in these non-trial patients. Patients with neuroendocrine or small cell differentiation were excluded unless their treatments occurred prior to pathological confirmation of neuroendocrine/small cell transdifferentiation.

HR repair gene status

Patients were sub-divided into two groups based on the presence or absence of HR repair gene mutations. The HR group contained patients with both somatic and germline mutations in genes involved in HR repair, including those indirectly regulating this pathway [5, 6, 27]. A broad set of genes was included given the recent approval of olaparib across an inclusive set of genes both directly and indirectly involved in HR repair [13, 17]. Monoallelic somatic mutations were considered sufficient for inclusion, given that many assays (e.g., FoundationOne) do not assess for loss of heterozygosity (LOH) or explicitly report germline mutations. Mutations were considered pathogenic if reported as such on the clinical report. Variants of unknown significance or otherwise benign changes were not included in the HR repair mutation cohort.

Data endpoints

The primary objective of this study was to determine the PSA50 and PSA30 response rate for each therapy, which was defined as the proportion of patients achieving $\geq$50% and $\geq$30% PSA reduction from the baseline PSA, respectively. Nadir PSA was recorded as the lowest PSA after starting treatment and prior to initiating a subsequent therapy.

The secondary objectives included determining PSA PFS (pPFS) and clinical/radiographic PFS (crPFS). PSA progression was defined by a PSA increase that was $\geq$2 ng/mL and $\geq$25% above the nadir on two consecutive lab draws. Clinical/radiographic progression was based on the assessment of the treating physician and was determined through chart review. Response Evaluation Criteria in Solid Tumors (RECIST) criteria were not utilized given that most patients were not treated on a clinical trial.

Statistical analysis

Differences in demographic characteristics and baseline laboratory measurements between the two populations were evaluated using Kruskal-Wallis or Fisher's exact tests. Differences in PSA50 and PSA30 between populations were evaluated using Fisher's exact tests separately for each treatment modality. Kaplan-Meier curves were calculated for pPFS and crPFS for each treatment modality, and differences between populations were evaluated using log-rank tests. A p-value <0.05 was considered statistically significant. All analyses were carried out using R statistical software version 3.6.3.

A secondary analysis estimated probabilities of PSA30/PSA50 using Bayesian logistic regression to adjust for prior receipt of similar therapy. Adjustment for prior similar therapy was examined given numerous studies highlighting varying levels of cross-resistance in these treatment modalities [28–32]. Prior similar therapy was defined as prior receipt of abiraterone or enzalutamide when either ARSI treatment was analyzed and prior receipt of docetaxel or cabazitaxel when either taxane-based chemotherapy was analyzed.

An exploratory analysis compared outcomes specifically for patients with *BRCA2* and *PALB2* mutations to those without HR repair gene mutations. Previous literature has demonstrated that these genes are closely associated with HR repair functional status [33, 34] and appear to be important predictive biomarkers for determining eligibility for DNA damaging agents. PSA30/PSA50 and pPFS/crPFS outcomes were re-evaluated for these comparisons.

Results

Patients

A total of 90 consecutively selected patients were included in this analysis, with HR repair gene mutations identified in 33/90 (37%). Of the 20 patients who underwent dedicated germline testing, 5 (25%) were found to harbor germline HR repair alterations. Mutations were found in 8 unique HR repair genes, with *BRCA2* (n = 16) being the most frequently altered (Table 1, S1 Table). A demographic comparison based on HR status showed similarity in age at diagnosis, Gleason score, prior surgery, and receipt of prior radiation therapy between the two patient populations (Table 2). Over 21% of patients with HR repair mutations were non-white in comparison to 7.1% of patients without HR repair mutations, although this finding did not reach statistical significance (p = 0.07). Laboratory parameters assessed prior to starting each treatment were also similar between the populations (S2–S5 Tables).

Efficacy outcomes

Best PSA response among patients with/without HR repair gene mutations is depicted in Fig 1 using waterfall plots for each treatment modality. Most patients achieved a PSA reduction from baseline in every treatment group except for patients without HR repair mutations treated with cabazitaxel. There was no evidence that PSA30 or PSA50 differed based on HR status for any treatment modality (Table 3). The frequency of patients achieving PSA50 in the population with HR repair gene mutations was 26% higher in the enzalutamide group and 40% higher in the cabazitaxel group compared to patients with no HR repair gene mutations, though neither result was statistically significant (p = 0.09 and p = 0.07, respectively). Regardless of HR repair gene mutation status, the PSA30 response rate was >50% and PSA50 response rate was >40% for all treatment modalities except cabazitaxel. Adjusting for prior similar therapy did not reveal an association between HR repair gene mutation status and PSA30/PSA50 for any of the treatments (S6 Table).

Kaplan-Meier curves of pPFS and crPFS are provided in Fig 2 by treatment modality. Median pPFS ranged between 2.8–6.5 months and median crPFS ranged between 4.2–14.2 months across treatment groups. There was no evidence that pPFS or crPFS differed based on HR repair gene mutation status for any treatment modality (Table 4).

Exploratory analyses comparing patients with mutations in *BRCA2* or *PALB2* to patients without HR repair mutations did not reveal differences in PSA30/PSA50 or pPFS/crPFS for any treatment (S1 and S2 Figs, S7 and S8 Tables), although the sample size within any molecular subgroup was small.

Discussion

The principal impetus behind this study was to evaluate whether mCRPC patients harboring mutations both directly and indirectly involved in HR repair achieve comparable outcomes to patients without such mutations following treatment with conventional, regulatory-approved treatment regimens. Given the recent FDA approvals of the PARP inhibitors rucaparib and olaparib, as well as interest in developing platinum-based chemotherapy for patients with HR

Table 1. Complete list of HR mutations.

Study ID	Sequencing Assay	Affected HR Gene	Germline alteration?	Bi-allelic mutation?
1	UW-OncoPlex	*FANCA*	N/A	No
2	WEC	*BRCA2*	No	Yes
4	UW-OncoPlex	*BRCA2*	N/A	Yes
9	UW-OncoPlex	*MRE11A*	N/A	No
14	UW-OncoPlex	*BRCA2*	No	Yes
20	UW-OncoPlex	*BRCA2*	No	Yes
24	FoundationOne, Color	*BRCA2*	Yes	Yes
25	UW-OncoPlex	*CDK12*	N/A	Yes
27	UW-OncoPlex	*BRCA2*	N/A	No
28	UW-OncoPlex, WEC	*BRCA2*	Yes	Yes
31	UW-OncoPlex	*BRCA2*	N/A	Yes
33	UW-OncoPlex	*BRCA2*	N/A	No
34	UW-OncoPlex	*CDK12*	N/A	Yes
36	FoundationOne	*ATM*	N/A	Yes
38	UW-OncoPlex	*PALB2*	N/A	Yes
39	UW-OncoPlex	*CHD1*	N/A	No
43	UW-OncoPlex	*BRCA2*	N/A	N/A
44	Color	*BRCA2*	Yes	N/A
48	UW-OncoPlex	*CHD1*	N/A	Yes
57	FoundationOne	*CDK12*	N/A	Yes
59	UW-OncoPlex	*BRCA2*	N/A	Yes
63	BRACAnalysis	*BRCA2*	Yes	N/A
69	UW-OncoPlex	*CHD1*	N/A	Yes
70	UW-OncoPlex	*ATM*	N/A	No
71	UW-OncoPlex	*FANCA*	N/A	N/A
72	UW-OncoPlex	*CDK12*	N/A	N/A
78	Guardant360, FoundationOne, Color	*BRCA2*	Yes	N/A
79	UW-OncoPlex	*CHD1*	N/A	Yes
81	FoundationOne	*ATM*	No	No
82	GeneTrails	*FANCA*	N/A	N/A
84	UW-OncoPlex	*BRCA2*	N/A	Yes
86	UW-OncoPlex	*MRE11A*	N/A	Yes
90	UW-OncoPlex	*BRCA2*, *CHEK2*	N/A	Yes

"WEC" denotes the Whole Exome Sequencing assay.

https://doi.org/10.1371/journal.pone.0239686.t001

repair gene mutations, we felt it was imperative to examine whether current conventional mCRPC treatments retain efficacy in this patient population. Our findings of similar PSA response and PFS in patients with HR repair gene mutations treated with ARSIs and taxane-based chemotherapy suggests that current standard mCRPC treatments are still very reasonable options for this patient population.

Our data largely aligns with the results of the recently published PROREPAIR-B study, which found non-significant differences in PSA50, PFS, and cause-specific survival when comparing germline *ATM/BRCA1/BRCA2/PALB2* carriers to non-carriers [35]. In contrast to the PROREPAIR-B study, which reported decreased survival in men with *BRCA2* mutations in a post hoc analysis, we did not observe survival differences in those with *BRCA2* mutations; although, our small sample size limited our statistical power to detect differences in outcomes.

Table 2. Patient characteristics by HR status.

Measure	No HR (N = 57)	HR (N = 33)	P-value
Age, years, median [IQR]	61.1 [55.2, 66.4]	61.0 [53.0, 67.5]	0.8
Race, N (%)			
• White	53 (93.0)	26 (78.8)	0.07
• Black	1 (1.8)	4 (12.1)	
• Asian/Unknown	3 (5.3)	3 (9.1)	
Gleason Score, N (%)			
• 6	2 (3.5)	0 (0.0)	0.6
• 7	20 (35.1)	10 (30.3)	
• 8–10	31 (54.4)	22 (66.7)	
• Unknown	4 (7.0)	1 (3.0)	
Prior Surgery, N (%)			
• No	31 (54.4)	20 (60.6)	0.4
• Yes	26 (45.6)	12 (36.4)	
• Unknown	0 (0.0)	1 (3.0)	
Prior Radiation Therapy, N (%)			
• No	14 (24.6)	12 (36.4)	0.6
• Yes	29 (50.9)	15 (45.5)	
• Unknown	14 (24.6)	6 (18.2)	

P-value for age from Kruskal-Wallis rank sum test and for other measures from Fisher's exact test.

https://doi.org/10.1371/journal.pone.0239686.t002

It does seem plausible that *BRCA1/2* and other proteins directly interacting with the *BRCA* complex may have distinct clinical and biologic relevance compared to those that indirectly regulate HR repair (e.g., *CDK12*, *ATM*, *CHEK2*). Indeed, results from TRITON2, TOPARP-B, and PROfound all suggest that responses to PARP inhibitors are largely observed in those with *BRCA* mutations [12, 13, 15]. These observations support the need to further examine clinical outcomes on an individual gene basis.

The 37% overall HR repair gene mutation rate found within our population is significantly higher than what has been reported in previous studies. It is important to emphasize that our research was not designed to characterize the frequency of HR repair gene mutations within mCRPC patients, but rather to assess clinical response in patients with such mutations. Our population was not cross-sectional and was enriched by our selection criteria. Specifically, our requirement of NGS likely inflated the frequency of HR repair gene mutations found, as NGS was more often performed in patients with significant family history, high-risk tumor histology (e.g., Gleason grade group 4–5 and ductal histology) [5, 36, 37], unique clinical course, or known germline variants.

A major limitation of this study was its small sample size. With 90 total patients and relatively small numbers in each treatment modality, our analyses were underpowered to detect small differences in outcomes. Limited patient numbers also precluded additional sub-analyses, including comparisons of germline versus somatic mutations, monoallelic versus biallelic mutations, and *BRCA1/2*-mutated versus other HR repair gene alterations. We also used a permissive approach for classifying HR repair deficiency. This approach was largely pragmatic in nature and resembles the 'real world' data most practicing oncologists use to make treatment choices given that many NGS platforms do not report LOH events or germline alterations. Until such data becomes more readily reported and operational for providers, our data indicates that standard therapies for mCRPC (i.e. non-DDR-targeted treatments such as ARSIs and taxane chemotherapy) should still be considered for these patients.

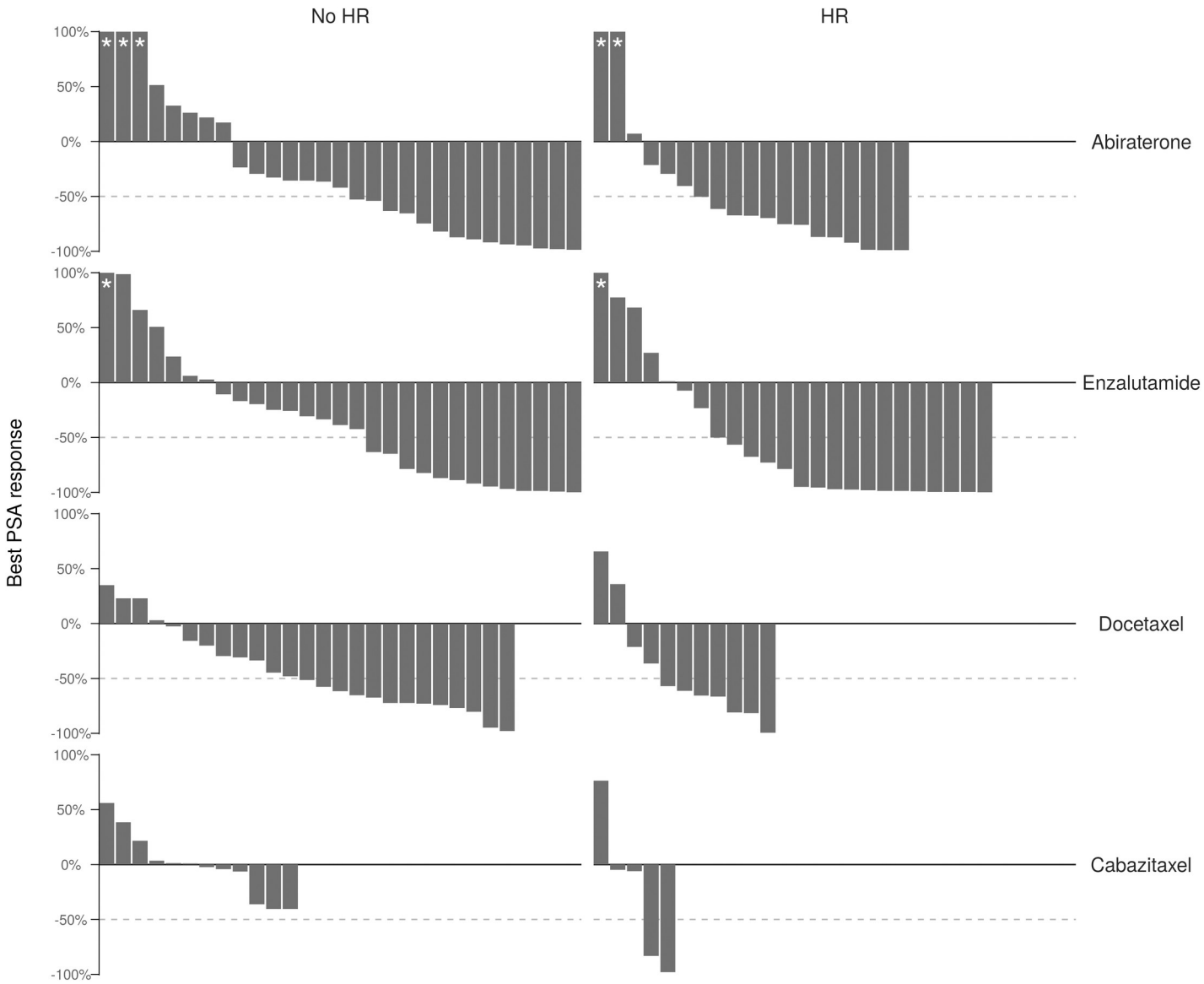


Fig 1. Waterfall plot of best PSA response by treatment and HR status. Maximum percent relative change from baseline during treatment or after completing treatment but prior to subsequent treatment. Maximum percent change greater than 100% is truncated at 100%. Dashed horizontal lines show 50% decrease.

https://doi.org/10.1371/journal.pone.0239686.g001

Table 3. Best PSA response by treatment and HR status.

Treatment	Response	No HR, N (%)	HR, N (%)	P-value
Abiraterone	PSA30	19/29 (66%)	14/19 (74%)	0.8
	PSA50	14/29 (48%)	13/19 (68%)	0.2
Enzalutamide	PSA30	17/29 (59%)	17/24 (71%)	0.4
	PSA50	13/29 (45%)	17/24 (71%)	0.09
Docetaxel	PSA30	17/25 (68%)	8/11 (73%)	1.0
	PSA50	13/25 (52%)	7/11 (64%)	0.7
Cabazitaxel	PSA30	3/12 (25%)	2/5 (40%)	0.6
	PSA50	0/12 (0%)	2/5 (40%)	0.07

PSA50 is 50% decrease in PSA relative to baseline. PSA30 is 30% decrease in PSA relative to baseline. P-values from Fisher's exact test.

https://doi.org/10.1371/journal.pone.0239686.t003

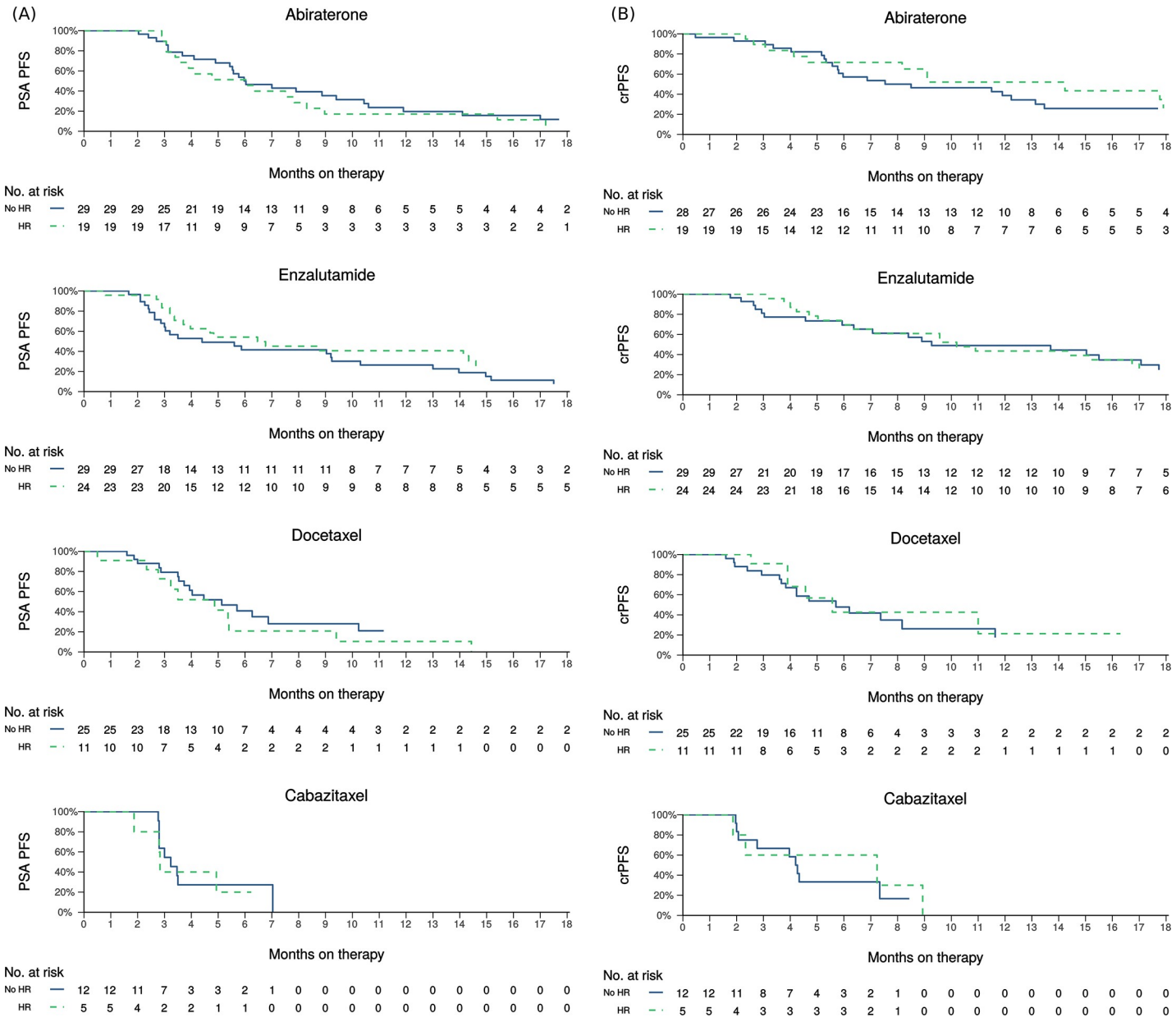


Fig 2. Kaplan-Meier curves of (A) PSA progression-free survival and (B) clinical or radiographic progression-free survival by treatment and HR status.

https://doi.org/10.1371/journal.pone.0239686.g002

The retrospective nature of this study provided its own set of challenges. NGS was performed at variable times during clinical courses, so HR repair gene mutation status may have been unknown at the time of treatment in many patients. While some data suggests that HR repair gene mutations are typically early (i.e. truncal) genomic events, we cannot rule out the possibility that some patient had their HR gene mutational status misclassified [38]. Additionally, when assessing PFS endpoints, we did not require confirmation of PSA or clinical/radiographic progression. No central review was performed, and there were no preset criteria for the evaluation of progression events. PFS outcomes were also dependent on the intervals at which clinical markers for progression were assessed. Whereas a prospective trial could standardize the frequency of clinical evaluations across all patients, ours were entirely provider dependent.

Table 4. Median (A) PSA progression-free survival and (B) clinical or radiographic progression-free survival by treatment and HR status.

A) PSA progression-free survival (pPFS)				
Treatment	**HR Status**	**N**	**Median pPFS (95% CI)**	**P-value**
Abiraterone	No HR	29	6.0 (5.4, 10.6)	0.4
	HR	19	6.1 (3.9, 9.0)	
Enzalutamide	No HR	29	4.4 (3.0, 10.3)	0.15
	HR	24	6.5 (4.0, 24.0)	
Docetaxel	No HR	25	5.1 (3.7, NA)	0.2
	HR	11	4.9 (3.2, NA)	
Cabazitaxel	No HR	12	3.2 (2.8, NA)	0.7
	HR	5	2.8 (2.8, NA)	
(B) Clinical or radiographic progression-free survival (crPFS)				
Treatment	**HR Status**	**N**	**Median crPFS (95% CI)**	**P-value**
Abiraterone	No HR	28	8.0 (5.8, 13.5)	0.6
	HR	19	14.2 (8.2, NA)	
Enzalutamide	No HR	29	9.3 (6.4, 19.3)	0.5
	HR	24	10.2 (6.2, 19.5)	
Docetaxel	No HR	25	5.7 (4.2, NA)	0.7
	HR	11	5.6 (3.9, NA)	
Cabazitaxel	No HR	12	4.2 (2.8, NA)	0.6
	HR	5	7.2 (2.3, NA)	

P-values from log-rank tests. NA = not achieved.

https://doi.org/10.1371/journal.pone.0239686.t004

Another potential constraint was our exclusion of treatments lasting less than 60 days. Consistent with PCWG3 guidelines, our intent was to only evaluate patients who had received a sufficient duration of treatment to determine if they would achieve any therapeutic response. In this regard, patients who may have been taken off therapy prematurely for rising PSA values or symptoms consistent with clinical progression would not obscure the remainder of the data set. However, if there happened to be an association between HR repair gene status and frequency of early-onset progression events, it could be indicative of a bias that was manufactured through our inclusion criteria.

Future directions should include an effort to more definitively describe treatment responses in mCRPC patients with HR repair gene mutations using larger, prospective trials with standardized clinical outcomes. In addition, more granular outcomes data for each specific HR repair gene are needed to determine which are predictive and prognostic biomarkers.

Conclusion

In our retrospective analysis of patients with mCRPC, HR repair gene mutational status associated with similar PSA response and PFS following treatment with ARSIs and taxane-based chemotherapy. Available data suggests that standard therapies should still be considered for patients with HR repair gene mutations. Additional prospective and larger studies are needed to confirm these findings.

Supporting information

S1 Fig. Waterfall plot of best PSA response by treatment and HR status (BRCA2 or PALB2 vs no HR). Maximum percent relative change from baseline during treatment or after

completing treatment but prior to subsequent treatment. Maximum percent change greater than 100% is truncated at 100%. Dashed horizontal lines show 50% decrease.
(TIF)

S2 Fig. Kaplan-Meier curves of (A) PSA progression-free survival and (B) clinical or radiographic progression-free survival by treatment and HR status (BRCA2 or PALB2 vs no HR).
(TIFF)

S1 Table. Specific genetic variants of every patient included in the HR cohort. "WEC" denotes the Whole Exome Sequencing assay.
(PDF)

S2 Table. Baseline lab comparisons at start of abiraterone based on HR status. P-values for continuous measures from Kruskal-Wallis rank sum test and for categorical measures from Fisher's exact test.
(PDF)

S3 Table. Baseline lab comparisons at start of enzalutamide based on HR status. P-values for continuous measures from Kruskal-Wallis rank sum test and for categorical measures from Fisher's exact test.
(PDF)

S4 Table. Baseline lab comparisons at start of docetaxel based on HR status. P-values for continuous measures from Kruskal-Wallis rank sum test and for categorical measures from Fisher's exact test.
(PDF)

S5 Table. Baseline lab comparisons at start of cabazitaxel based on HR status. P-values for continuous measures from Kruskal-Wallis test rank sum and for categorical measures from Fisher's exact test.
(PDF)

S6 Table. Predicted probabilities of (A) PSA30 and (B) PSA50 adjusted for prior treatment with similar therapy.
(PDF)

S7 Table. Best PSA response by treatment and HR status (BRCA2 or PALB2 vs no HR). PSA50 is 50% decrease in PSA relative to baseline. PSA30 is 30% decrease in PSA relative to baseline. P-values from Fisher's exact test.
(PDF)

S8 Table. Median (A) PSA progression-free survival and (B) clinical or radiographic progression-free survival by treatment and HR status (BRCA2 or PALB2 vs no HR). P-values from log-rank tests. NA = not achieved.
(PDF)

Acknowledgments

We are grateful for the patients who participated in this study.

Author Contributions

Conceptualization: Alexander S. Carlson, Rigo I. Acevedo, Alexandra O. Sokolova, Heather H. Cheng, Peter S. Nelson, R. Bruce Montgomery, Evan Y. Yu, Michael T. Schweizer.

Data curation: Alexander S. Carlson, Rigo I. Acevedo, Daniel M. Lim, Roman Gulati, Agnes Gawne, Evan Y. Yu, Michael T. Schweizer.

Formal analysis: Alexander S. Carlson, Daniel M. Lim, Roman Gulati.

Funding acquisition: Evan Y. Yu, Michael T. Schweizer.

Investigation: Alexander S. Carlson, Rigo I. Acevedo, Daniel M. Lim, Evan Y. Yu, Michael T. Schweizer.

Methodology: Alexander S. Carlson, Rigo I. Acevedo, Alexandra O. Sokolova, Heather H. Cheng, Peter S. Nelson, R. Bruce Montgomery, Evan Y. Yu, Michael T. Schweizer.

Project administration: Alexander S. Carlson, Evan Y. Yu, Michael T. Schweizer.

Resources: Roman Gulati, Agnes Gawne, Peter S. Nelson, Evan Y. Yu, Michael T. Schweizer.

Software: Roman Gulati, Agnes Gawne.

Supervision: Evan Y. Yu, Michael T. Schweizer.

Validation: Roman Gulati, Evan Y. Yu, Michael T. Schweizer.

Visualization: Alexander S. Carlson, Roman Gulati.

Writing – original draft: Alexander S. Carlson.

Writing – review & editing: Alexander S. Carlson, Rigo I. Acevedo, Daniel M. Lim, Roman Gulati, Alexandra O. Sokolova, Heather H. Cheng, Peter S. Nelson, R. Bruce Montgomery, Evan Y. Yu, Michael T. Schweizer.

References

1. Torgovnick A, Schumacher B. DNA repair mechanisms in cancer development and therapy. Frontiers in genetics. 2015; 6:157. https://doi.org/10.3389/fgene.2015.00157 PMID: 25954303
2. Baretta Z, Mocellin S, Goldin E, Olopade OI, Huo D. Effect of *BRCA* germline mutations on breast cancer prognosis: A systematic review and meta-analysis. Medicine. 2016; 95(40):e4975. https://doi.org/10.1097/MD.0000000000004975 PMID: 27749552
3. Castro E, Goh C, Olmos D, Saunders E, Leongamornlert D, Tymrakiewicz M, et al. Germline *BRCA* mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. J Clin Oncol. 2013; 31(14):1748–57. https://doi.org/10.1200/JCO.2012.43.1882 PMID: 23569316
4. Castro E, Goh C, Leongamornlert D, Saunders E, Tymrakiewicz M, Dadaev T, et al. Effect of *BRCA* Mutations on Metastatic Relapse and Cause-specific Survival After Radical Treatment for Localised Prostate Cancer. Eur Urol. 2015; 68(2):186–93. https://doi.org/10.1016/j.eururo.2014.10.022 PMID: 25454609
5. Robinson D, Van Allen EM, Wu YM, Schultz N, Lonigro RJ, Mosquera JM, et al. Integrative Clinical Genomics of Advanced Prostate Cancer. Cell. 2015; 162(2):454. https://doi.org/10.1016/j.cell.2015.06.053 PMID: 28843286
6. Pritchard CC, Mateo J, Walsh MF, De Sarkar N, Abida W, Beltran H, et al. Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer. The New England journal of medicine. 2016; 375(5):443–53. https://doi.org/10.1056/NEJMoa1603144 PMID: 27433846
7. Schweizer MT, Antonarakis ES. Prognostic and therapeutic implications of DNA repair gene mutations in advanced prostate cancer. Clinical advances in hematology & oncology: H&O. 2017; 15(10):785–95.
8. D'Andrea AD. Mechanisms of PARP inhibitor sensitivity and resistance. DNA repair. 2018; 71:172–6. https://doi.org/10.1016/j.dnarep.2018.08.021 PMID: 30177437
9. Konstantinopoulos PA, Ceccaldi R, Shapiro GI, D'Andrea AD. Homologous Recombination Deficiency: Exploiting the Fundamental Vulnerability of Ovarian Cancer. Cancer discovery. 2015; 5(11):1137–54. https://doi.org/10.1158/2159-8290.CD-15-0714 PMID: 26463832
10. Scott CL, Swisher EM, Kaufmann SH. Poly (ADP-ribose) polymerase inhibitors: recent advances and future development. J Clin Oncol. 2015; 33(12):1397–406. https://doi.org/10.1200/JCO.2014.58.8848 PMID: 25779564

11. Mateo J, Carreira S, Sandhu S, Miranda S, Mossop H, Perez-Lopez R, et al. DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer. The New England journal of medicine. 2015; 373(18):1697–708. https://doi.org/10.1056/NEJMoa1506859 PMID: 26510020

12. Mateo J, Porta N, Bianchini D, McGovern U, Elliott T, Jones R, et al. Olaparib in patients with metastatic castration-resistant prostate cancer with DNA repair gene aberrations (TOPARP-B): a multicentre, open-label, randomised, phase 2 trial. The Lancet Oncology. 2020; 21(1):162–74. https://doi.org/10.1016/S1470-2045(19)30684-9 PMID: 31806540

13. de Bono J, Mateo J, Fizazi K, Saad F, Shore N, Sandhu S, et al. Olaparib for Metastatic Castration-Resistant Prostate Cancer. The New England journal of medicine. 2020.

14. Marshall CH, Sokolova AO, McNatty AL, Cheng HH, Eisenberger MA, Bryce AH, et al. Differential Response to Olaparib Treatment Among Men with Metastatic Castration-resistant Prostate Cancer Harboring *BRCA1* or *BRCA2* Versus *ATM* Mutations. Eur Urol. 2019; 76(4):452–8. https://doi.org/10.1016/j.eururo.2019.02.002 PMID: 30797618

15. Abida W, Campbell D, Patnaik A, Shapiro JD, Sautois B, Vogelzang NJ, et al. Non-*BRCA* DNA Damage Repair Gene Alterations and Response to the PARP Inhibitor Rucaparib in Metastatic Castration-Resistant Prostate Cancer: analysis from the phase 2 TRITON2 study. Clinical cancer research: an official journal of the American Association for Cancer Research. 2020.

16. FDA grants accelerated approval to rucaparib for *BRCA*-mutated metastatic castration-resistant prostate cancer. U.S. Food and Drug Administration. 2020. Available from: https://www.fda.gov/drugs/fda-grants-accelerated-approval-rucaparib-brca-mutated-metastatic-castration-resistant-prostate

17. FDA approves olaparib for HRR gene-mutated metastatic castration-resistant prostate cancer. U.S. Food and Drug Administration. 2020. Available from: https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-olaparib-hrr-gene-mutated-metastatic-castration-resistant-prostate-cancer

18. Basu A, Krishnamurthy S. Cellular responses to Cisplatin-induced DNA damage. Journal of nucleic acids. 2010; 2010.

19. Cheng HH, Pritchard CC, Boyd T, Nelson PS, Montgomery B. Biallelic Inactivation of *BRCA2* in Platinum-sensitive Metastatic Castration-resistant Prostate Cancer. Eur Urol. 2016; 69(6):992–5. https://doi.org/10.1016/j.eururo.2015.11.022 PMID: 26724258

20. Pomerantz MM, Spisak S, Jia L, Cronin AM, Csabai I, Ledet E, et al. The association between germline *BRCA2* variants and sensitivity to platinum-based chemotherapy among men with metastatic prostate cancer. Cancer. 2017; 123(18):3532–9. https://doi.org/10.1002/cncr.30808 PMID: 28608931

21. Schweizer MT, Antonarakis ES. Chemotherapy and its evolving role in the management of advanced prostate cancer. Asian journal of andrology. 2014; 16(3):334–40. https://doi.org/10.4103/1008-682X.122593 PMID: 24435058

22. Hussain M, Daignault-Newton S, Twardowski PW, Albany C, Stein MN, Kunju LP, et al. Targeting Androgen Receptor and DNA Repair in Metastatic Castration-Resistant Prostate Cancer: Results From NCI 9012. J Clin Oncol. 2018; 36(10):991–9. https://doi.org/10.1200/JCO.2017.75.7310 PMID: 29261439

23. Annala M, Struss WJ, Warner EW, Beja K, Vandekerkhove G, Wong A, et al. Treatment Outcomes and Tumor Loss of Heterozygosity in Germline DNA Repair-deficient Prostate Cancer. Eur Urol. 2017; 72(1):34–42. https://doi.org/10.1016/j.eururo.2017.02.023 PMID: 28259476

24. Mateo J, Cheng HH, Beltran H, Dolling D, Xu W, Pritchard CC, et al. Clinical Outcome of Prostate Cancer Patients with Germline DNA Repair Mutations: Retrospective Analysis from an International Study. Eur Urol. 2018; 73(5):687–93. https://doi.org/10.1016/j.eururo.2018.01.010 PMID: 29429804

25. Gallagher DJ, Cronin AM, Milowsky MI, Morris MJ, Bhatia J, Scardino PT, et al. Germline *BRCA* mutation does not prevent response to taxane-based therapy for the treatment of castration-resistant prostate cancer. BJU international. 2012; 109(5):713–9. https://doi.org/10.1111/j.1464-410X.2011.10292.x PMID: 21756279

26. Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol. 2016; 34(12):1402–18. https://doi.org/10.1200/JCO.2015.64.2702 PMID: 26903579

27. Kari V, Mansour WY, Raul SK, Baumgart SJ, Mund A, Grade M, et al. Loss of CHD1 causes DNA repair defects and enhances prostate cancer therapeutic responsiveness. EMBO reports. 2018; 19(10).

28. Khalaf DJ, Annala M, Taavitsainen S, Finch DL, Oja C, Vergidis J, et al. Optimal sequencing of enzalutamide and abiraterone acetate plus prednisone in metastatic castration-resistant prostate cancer: a multicentre, randomised, open-label, phase 2, crossover trial. The Lancet Oncology. 2019; 20(12):1730–9. https://doi.org/10.1016/S1470-2045(19)30688-6 PMID: 31727538

29. Yamada Y, Matsubara N, Tabata KI, Satoh T, Kamiya N, Suzuki H, et al. Abiraterone acetate after progression with enzalutamide in chemotherapy-naive patients with metastatic castration-resistant

prostate cancer: a multi-center retrospective analysis. BMC research notes. 2016; 9(1):471. https://doi.org/10.1186/s13104-016-2279-9 PMID: 27756383

30. Cheng HH, Gulati R, Azad A, Nadal R, Twardowski P, Vaishampayan UN, et al. Activity of enzalutamide in men with metastatic castration-resistant prostate cancer is affected by prior treatment with abiraterone and/or docetaxel. Prostate cancer and prostatic diseases. 2015; 18(2):122–7. https://doi.org/10.1038/pcan.2014.53 PMID: 25600186

31. Al Nakouzi N, Le Moulec S, Albiges L, Wang C, Beuzeboc P, Gross-Goupil M, et al. Cabazitaxel Remains Active in Patients Progressing After Docetaxel Followed by Novel Androgen Receptor Pathway Targeted Therapies. Eur Urol. 2015; 68(2):228–35. https://doi.org/10.1016/j.eururo.2014.04.015 PMID: 24837187

32. Wissing MD, Coenen JL, van den Berg P, Westgeest HM, van den Eertwegh AJ, van Oort IM, et al. CAST: A retrospective analysis of cabazitaxel and abiraterone acetate sequential treatment in patients with metastatic castrate-resistant prostate cancer previously treated with docetaxel. International journal of cancer. 2015; 136(6):E760–72. https://doi.org/10.1002/ijc.29231 PMID: 25242736

33. Zhang F, Fan Q, Ren K, Andreassen PR. *PALB2* functionally connects the breast cancer susceptibility proteins *BRCA1* and *BRCA2*. Molecular cancer research: MCR. 2009; 7(7):1110–8. https://doi.org/10.1158/1541-7786.MCR-09-0123 PMID: 19584259

34. Xia B, Sheng Q, Nakanishi K, Ohashi A, Wu J, Christ N, et al. Control of *BRCA2* cellular and clinical functions by a nuclear partner, PALB2. Molecular cell. 2006; 22(6):719–29. https://doi.org/10.1016/j.molcel.2006.05.022 PMID: 16793542

35. Castro E, Romero-Laorden N, Del Pozo A, Lozano R, Medina A, Puente J, et al. PROREPAIR-B: A Prospective Cohort Study of the Impact of Germline DNA Repair Mutations on the Outcomes of Patients With Metastatic Castration-Resistant Prostate Cancer. J Clin Oncol. 2019; 37(6):490–503. https://doi.org/10.1200/JCO.18.00358 PMID: 30625039

36. Schweizer MT, Antonarakis ES, Bismar TA, Guedes LB, Cheng HH, Tretiakova MS, et al. Genomic Characterization of Prostatic Ductal Adenocarcinoma Identifies a High Prevalence of DNA Repair Gene Mutations. JCO precision oncology. 2019; 3.

37. Guedes LB, Antonarakis ES, Schweizer MT, Mirkheshti N, Almutairi F, Park JC, et al. *MSH2* Loss in Primary Prostate Cancer. Clinical cancer research: an official journal of the American Association for Cancer Research. 2017; 23(22):6863–74.

38. Mateo J, Seed G, Bertan C, Rescigno P, Dolling D, Figueiredo I, et al. Genomics of lethal prostate cancer at diagnosis and castration resistance. The Journal of clinical investigation. 2020; 130(4):1743–51. https://doi.org/10.1172/JCI132031 PMID: 31874108

HHS Public Access

Author manuscript

Clin Cancer Res. Author manuscript; available in PMC 2021 April 15.

Published in final edited form as:

Clin Cancer Res. 2020 October 15; 26(20): 5338–5347. doi:10.1158/1078-0432.CCR-20-1707.

A Phase 1b/2a Study of the Pan-BET Bromodomain Inhibitor ZEN-3694 in Combination with Enzalutamide in Patients with Metastatic Castration Resistant Prostate Cancer

Rahul Aggarwal[1], **Michael T. Schweizer**[2], **David M. Nanus**[3], **Allan Pantuck**[4], **Elisabeth Heath**[5], **Eric Campeau**[6], **Sarah Attwell**[6], **Karen Norek**[6], **Margo Snyder**[6], **Lisa Bauman**[6], **Sanjay Lakhotia**[6], **Felix Y. Feng**[1], **Eric J. Small**[1], **Wassim Abida**[*,7], **Joshi Alumkal**[*,8,9]

[1]University of California San Francisco, San Francisco, CA

[2]University of Washington and Fred Hutchinson Cancer Research Center, Seattle, WA

[3]Weill-Cornell Medicine, New York, NY

[4]University of California Los Angeles, Los Angeles, CA

[5]Karmanos Cancer Institute, Wayne State University, Detroit, MI

[6]Zenith Epigenetics Ltd., Calgary, Alberta, Canada

[7]Memorial Sloan Kettering Cancer Center, New York, NY

[8]Oregon Health & Science University, Portland, OR

[9]University of Michigan Rogel Cancer Center, Ann Arbor, MI

Abstract

Purpose—ZEN-3694 is a bromodomain extra-terminal inhibitor (BETi) with activity in androgen signaling inhibitor (ASI)-resistant models. The safety and efficacy of ZEN-3694 plus enzalutamide (ENZ) was evaluated in a phase 1b/2a study in metastatic castration-resistant prostate cancer (mCRPC).

Corresponding Authors: Rahul Aggarwal MD, 550 16th Street, San Francisco, CA 94158, Rahul.Aggarwal@ucsf.edu; Joshi Alumkal MD, 1500 E Medical Center Drive, Ann Arbor, MI 48109, jalumkal@med.umich.edu; Wassim Abida MD, 1275 York Avenue, New York, NY 10065, abidam@mskcc.org.

*Authors contributed equally

Disclosures:

RA has received consulting income from Janssen Biotech, Merck, AstraZeneca; research funding to his institution from Zenith Epigenetics; honoraria for speaker's fee from Dendreon and Clovis Oncology

MTS has received research funding to his institution from Janssen Biotech, AstraZeneca, Zenith Epigenetics, Pfizer, Madison Vaccines, and Hoffman-La Roche.

AP has received consulting income from Pfizer; founder and equity holder Athos Therapeutics; equity holder in Allogene, Urogen, and Clovis; serves on scientific advisory board for Attica Biosciences.

EC, SA, MS, LB, and SL are employed by drug manufacturer and sponsor Zenith Epigenetics, Ltd.

FYF has received research funding from Zenith Epigenetics; consulting income from Astellas, Blue Earth, Bayer, Clovis, Celgene, Janssen, Sanofi; and is co-founder of PFS Genomics.

WA has received consulting income from Clovis Oncology, Janssen Biotech, MORE Health, ORIC Pharmaceuticals, Daiichi Sankyo; research funding to his institution from AstraZeneca, Zenith Epigenetics, Clovis Oncology, and GlaxoSmithKline; honorarium from CARET

JJA has received consulting income from Janssen Biotech and Merck; honoraria for speaker's fees from Astella.

Experimental Design—Patients had progressive mCRPC with prior resistance to abiraterone (ABI) and/or ENZ. 3+3 dose escalation was followed by dose expansion in parallel cohorts (ZEN-3694 at 48 and 96 mg orally once daily, respectively).

Results—Seventy-five patients were enrolled (N = 26 and 14 in Dose Expansion at low- and high-dose ZEN-3694, respectively). Thirty (40.0%) patients were resistant to ABI, thirty-four (45.3%) to ENZ, and eleven (14.7%) to both. ZEN-3694 dosing ranged from 36 mg to 144 mg daily without reaching an MTD. Fourteen patients (18.7%) experienced grade ≥ 3 toxicities, including three patients with Grade 3 thrombocytopenia (4%). An exposure-dependent decrease in whole blood RNA expression of BETi targets was observed (up to 4-fold mean difference at 4 hours post-ZEN-3694 dose; $p \leq 0.0001$). The median radiographic progression-free survival (rPFS) was 9.0 months (95% CI: 4.6, 12.9) and composite median radiographic or clinical progression-free survival was 5.5 months (95% CI: 4.0, 7.8). Median duration of treatment was 3.5 months (range 0 – 34.7+). Lower AR transcriptional activity in baseline tumor biopsies was associated with longer rPFS (median rPFS 10.4 vs. 4.3 months).

Conclusions—ZEN-3694 plus ENZ demonstrated acceptable tolerability and potential efficacy in patients with ASI-resistant mCRPC. Further prospective study is warranted including in mCRPC harboring low AR transcriptional activity.

Introduction

Prostate cancer is the most common malignancy and second leading cause of death among men in the United States.[1] Androgen signaling blockade with either androgen receptor (AR) antagonism or CYP17 inhibition improves long-term survival in both metastatic castration-resistant prostate cancer (mCRPC) and metastatic castration-sensitive disease.[2–5] However treatment resistance is universal, and cross resistance between AR antagonists and CYP17 inhibitors limits the clinical utility of these agents when used sequentially.[6–10]

Multiple mechanisms of therapeutic resistance to AR pathway inhibitors have been described, including amplification of the *AR* gene and its enhancers, up-regulation of intra-tumoral androgen synthesis, generation of ligand-independent AR splice variants, activation of alternative oncogenic signaling pathways including MYC, trans-differentiation to an AR-independent, neuroendocrine phenotype, and co-option of alternative steroid hormone receptors including the glucocorticoid receptor (GR).[11–16] A broad therapeutic approach capable of affecting expression/signaling of multiple pathways may provide a means to reverse resistance and restore sensitivity to AR targeting therapy.

Proteins of the BET bromodomain family are epigenetic readers that bind to acetylated histones through their bromodomains to affect gene transcription.[17] They preferentially localize at sites of enhancers of various oncogenes to promote tumorigenesis and progression. ZEN-3694 is an orally bioavailable, second generation, potent pan-BET bromodomain inhibitor that leads to down-regulation of expression of AR-signaling, AR splice variants, MYC, GR, and other oncogenes in multiple CRPC prostate cancer models, and has significant *in vivo* activity as single agents, with evidence of synergy when combined with enzalutamide.[18]

We conducted a first-in-human phase 1b/2 dose escalation/expansion study of ZEN-3694 in combination with enzalutamide in patients with mCRPC and prior progression on one or more androgen signaling inhibitor.

METHODS

Patient Population

Patients had histologically confirmed mCRPC with progression at study entry by Prostate Cancer Working Group 2 (PCWG2) criteria.[19] Patients were required to have progression on prior abiraterone and/or enzalutamide prior to study entry, no prior docetaxel for the treatment of mCRPC, serum testosterone < 50 ng/dL with maintenance of androgen deprivation therapy during study treatment, ECOG performance status of 0 or 1, adequate organ function including absolute neutrophil count > 1.5×10^9/L, platelet count > 100,000, total bilirubin < 1.5 × ULN, creatinine clearance > 60 ml/min. Patients with uncontrolled hypertension or NYHA class II or higher congestive heart failure were excluded.

Study approval was obtained from the ethics committees at the participating institutions and regulatory authorities. All patients gave written informed consent. The study followed the Declaration of Helsinki and good clinical practice guidelines (NCT02711956).

Study Design and Treatment Schedule

This was a phase 1b/2, multicenter, open-label, combination dose-escalation study of ZEN-3694 in combination with the standard dose of enzalutamide 160 mg daily. Lead-in treatment period with enzalutamide monotherapy (day −14 to day −1) was required in subjects not already receiving enzalutamide at the time of study enrollment. Patients continued treatment until radiographic progression by PCWG2 criteria, unequivocal clinical progression or unacceptable toxicity. PSA progression alone was not used as a criterion for treatment discontinuation.

The starting dose of ZEN-3694 was 36 mg orally once daily. A 3+3 dose-escalation schema was utilized up to a maximum administered dose of 144 mg daily. Dose expansion was subsequently performed in two cohorts in parallel: 1) Low dose: ZEN-3694 at 48 mg daily (N = 14), and 2) High dose ZEN-3694 96 mg daily (N = 26).

A formal interim analysis was not planned, however interim data were reviewed on an ongoing basis. The final planned analyses were performed after 75 patients were enrolled and the database was locked on 06-Feb-2020.

The primary study endpoint was safety and the recommended phase 2 dose of ZEN-3694 in combination with enzalutamide. Secondary endpoints included pharmacokinetic (PK) assessment of ZEN-3694 and enzalutamide, PSA50 response (≥50% decline in PSA from baseline confirmed ≥ 4 weeks later) rate, duration of PSA50 response, and radiographic progression-free survival. Soft tissue radiographic progression and responses were assessed according to RECIST v1.1 criteria. Progression of bone metastases was assessed using PCWG2 criteria. Post-hoc analyses were performed to assess composite progression-free survival, defined as first occurrence of radiographic or clinical progression or death, as well

as PSA progression-free survival by PCWG2 criteria. Correlative endpoints included pharmacodynamic assessment of ZEN-3694 in combination with enzalutamide and relationship between tumor genomic/transcriptional profile, protein expression, and clinical variables with clinical outcomes on treatment.

Safety and Efficacy Assessments

Clinical and laboratory assessments were conducted at baseline and weekly during cycles 1 and 2 (28 day cycle length), every 2 weeks in cycle 3, and then every 4 weeks thereafter. Tumor response monitoring was performed using whole body bone scan and cross-sectional imaging of the chest/abdomen/pelvis at baseline and every 2 cycles thereafter. Adverse events were graded using Common Toxicity Criteria version 4.0.

Pharmacodynamic/Exploratory Assessments

Whole blood RNA for assessment of BET inhibitor target gene expression (*MYC*, *IL-8*, *CCR1*, GPR183, HEXIM1, and *IL1RN*) was collected pre-dose, 2, 4, 6 and 24 hours post-C1D1 dose.[20] Baseline and on-treatment metastatic tumor biopsies of bone or soft tissue were obtained whenever feasible, and were evaluated by RNA-seq and immunohistochemistry (IHC) for protein expression of AR. Quality of the FASTQ files was verified by FASTQC2, and reads were aligned on BaseSpace (https://basespace.illumina.com) using the RNA-Seq alignment App (version 1.1.1) with the default parameters (STAR aligner version 2.5.0b, UCSC hg19 reference genome). Gene expression levels (FPKM) for baseline biopsies were estimated using Cufflinks (version 2.2.1). For the paired biopsies, aligned reads were used as input for DESeq2 (version 1.1.0) to enable pairwise differential gene expression analysis using the default parameters. Gene set enrichment analysis (GSEA) was performed on transcriptional data when available, and previously validated AR, prostate cancer and MYC transcriptional signatures were additionally applied to the transcriptional data.[21–22] For the BETi signature, significant genes (p-value <0.05) that were >2-fold down-regulated upon exposure of 0.5uM I-BET762 for 24 hours in LNCaP prostate cancer cells were selected.[23] Archival tumor tissue was obtained whenever feasible for analysis of whole transcriptome and exome sequencing.

Pharmacokinetic Assessments

Plasma levels of ZEN-3694, the bioactive first-order metabolite ZEN-3791, and enzalutamide were measured pre-dose and up to 24 hours post-dose on days 1 and 15 of cycle. Plasma concentrations were determined using validated liquid chromatography/tandem mass spectrometry analysis (LC/MS/MS).

RESULTS

Study Population and Patient Disposition

A total of 75 patients were enrolled from December 2016 to April 2019 across 7 investigational sites. Baseline characteristics of the enrolled patients are shown in Table 1. At study entry, 30 (40.0%) of patients had previously experienced disease progression on abiraterone, 34 (45.3%) on enzalutamide, and 11 (14.7%) on both. Twelve (16%) patients experienced prior primary resistance to first-line AR targeted therapy, defined in post-hoc

fashion as treatment duration of less than six months. Forty-two (56%) patients had evidence of radiographic and/or clinical progression at study entry.

The median duration of treatment was 3.5 months (range 0 – 34.7+). As of date of data cut-off, 7 patients (9%) remain on treatment without progression, with duration of therapy ranging from 15.0+ – 34.7+ months. Forty-eight patients (64%) discontinued for disease progression; nine patients (12%) discontinued for adverse event, and eleven (16%) withdrew from study.

Safety Results

The proportion of patients who experienced Grade ≥ 3 treatment-related adverse event was 18.7% (n = 14). The most common grade ≥ 3 adverse events (≥ 2 patients) included: nausea (n = 3; 4 %), thrombocytopenia (n = 3; 4%), anemia (n = 2; 2.7%), fatigue (n = 2; 2.7%), and hypophosphatemia (n = 2; 2.7%). There were no clinically significant bleeding events observed on treatment.

The most commonly reported ZEN003694-related AEs (any grade severity, occurring in ≥ 10% of patients, in order of incidence) were: visual symptoms (described as a transitory perception of brighter lights and/or light flashes, with or without visual color tinges, as well as trouble navigating in dim light) (67%), nausea (45%), fatigue (40%), decreased appetite (25%), dysgeusia (20%), thrombocytopenia (15%), and weight decreased (11%) (Table 2). Visual symptoms were Grade 1 in all cases, resolved 60–90 minutes after dosing, were successfully mitigated with implementation of dosing before bedtime, and resulted in no functional consequences upon repeat eye exams throughout study participation.

Dose reductions and/or treatment discontinuation due to adverse events were required in 24/75 (32%) of patients. The percentage of patients requiring dose reduction and/or discontinuation ranged from 10%−35% for doses from 36 mg – 96 mg/day, in contrast to 75% and 100% at ZEN-3694 dose levels of 120 and 144 mg/day, respectively (Supplementary Table 1). The class of adverse events leading to dose reduction and/or discontinuation were related to GI toxicities in 83% of occurrences.

Determination of Maximum Tolerated Dose and Recommended Phase 2 Dose

In the dose escalation, 35 patients were enrolled across dose levels ranging from 36 to 144 mg daily. The maximal tolerated dose was not reached. One patient experienced a dose-limiting toxicity at the 96 mg/day dose level (Grade 3 nausea necessitating missing > 25% of scheduled doses in cycle 1). Based on the aggregate of pharmacodynamic data indicating dose exposure-dependent down-regulation of BETi target gene expression with a plateau of effect at doses above 96 mg/day, the high percentage of patients requiring dose interruptions/reductions at doses above 96 mg/day, and a comparable PK/PD effect with pre-clinical models treated at efficacious doses, 96 mg/day was chosen as the recommended phase 2 dose of ZEN-3694 for Dose Expansion (N = 26). An additional Dose Expansion cohort of 48 mg/day (N = 14) was also enrolled, to better characterize the exposure-effect relationship.

Pharmacokinetic Analyses

The $AUC_{0–24}$ and the C_{max} of combined ZEN-3694 (parent compound) + ZEN-3791 (active metabolite), on Day 1 and Day 15 of cycle 1, are shown in Figure 1A and Figure 1B, respectively. Less than dose proportional increase in exposure was observed at doses higher than 96 mg daily. The estimated T_{max} and half-life of ZEN-3694+ZEN-3791 were 2h and 5–6h, respectively. The ratio of ZEN-3791 metabolite to parent compound ZEN-3694 was increased on Day 15 compared to Day 1, likely related to enzalutamide-mediated induction of CYP3A4 metabolism (Figure 1C). The observed plasma concentrations of ZEN-3694 + ZEN-3791 were similar to ZEN-3694 monotherapy pharmacokinetics previously reported.[24] Likewise, there was no significant impact of ZEN-3694 on enzalutamide and desmethyl enzalutamide concentrations (Figure 1D).

Pharmacodynamic Analyses

Pre- and up to 24 hour post-dose whole blood RNA analyses were available from 69 patients enrolled on study. There was a dose-dependent 2–4 fold decrease in the whole blood mRNA levels of the BET inhibitor target genes *MYC*, *IL-8*, *CCR1*, GPR183, and *IL1RN* (Figure 2A) upon treatment with ZEN-3694, which was sustained for at least 8 hours. Decrease in expression of BET inhibitor target genes appeared to plateau at ZEN-3694 dose levels ≥ 96 mg. There was a direct correlation between cumulative exposure to ZEN-3694 + ZEN-3791 ($AUC_{0–2}$ for *MYC* and *GPR183*, and $AUC_{0–4}$ for *CCR1*, *IL1RN*, and *IL-8*) with down-regulation of whole blood mRNA levels of the BET inhibitor target genes (R^2 ranging from 0.20 to 0.51, p values ≤ 0.0001) (Figure 2B).

Four patients had evaluable paired metastatic tumor biopsies obtained at baseline and on-treatment (median duration of treatment eight weeks prior to on-treatment biopsy). Time after the last ZEN-3694 + enzalutamide dosing prior to the biopsy ranged from 3.5 to 24 hours. The limited sample size precluded ability to perform statistical analyses of change in expression by dose level. However, on gene set enrichment analyses looking at changes between on-treatment versus pre-treatment samples, there were strong indications of down-regulation of expression of MYC and AR-signaling on-treatment compared to baseline biopsies were detected, as well as down-regulation of BET-dependent genes previously identified in LnCaP cells treated with the I-BET762 BET inhibitor[23] (Figure 2C).

Efficacy Analyses

The median radiographic progression-free survival (rPFS) in the overall cohort was 9.0 months (95% CI: 4.6, 12.9), with 7.8 months for patients that had progressed on abiraterone (95% CI: 4.9, 10.6) and 10.1 months for patients that had progressed on enzalutamide (95% CI: 4.4, 12.9) (Figure 3A). Composite median radiographic or clinical progression-free survival was 5.5 months (95% CI: 4.0, 7.8) in the overall cohort, and 5.5 months (95% CI: 4.4, 7.8) and 5.1 months (95% CI: 3.2, 10.1) in those with prior progression on abiraterone and enzalutamide, respectively (Figure 3B). Thirteen (17%) and four (5%) patients remained on treatment for greater than 12 and 24 months without progression, respectively (Figure 3C). In patients with radiographic progression at the time of study entry, the median rPFS was 7.8 months (95% CI: 4.4, 10.6) (Figure 3D) and composite PFS was 4.8 months (95% CI: 3.5, 7.7). An analysis of the subset of patients with primary resistance to prior first-line

AR targeted therapy (N = 12), defined by progression within 6 months of treatment initiation, demonstrated an on-treatment median rPFS of 10.6 months (95% CI (7.5, not reached) (Figure 3E). Using a more stringent cut-off of primary resistance of progression within 16 weeks of prior first-line AR targeted therapy (N = 5) likewise demonstrated prolonged median rPFS (median rPFS 22.4 months, 95% CI: 7.8, not reached) and composite PFS (median PFS 10.6 months, 95% CI: 4.0, not reached) in this subset of patients (Supplementary Figure 1A and 1B).

Of the four exceptional responders who remained on treatment for greater than 24 months duration, three had radiographic progression at study entry, two had progressed on prior enzalutamide, and one of the four patients experienced an objective radiographic response on enzalutamide + ZEN-3694 (Supplementary Table 2).

Six patients (8%) experienced a greater than fifty percent decline from baseline in serum PSA by PCWG2 criteria (PSA50 response), including two patients with prior progression on enzalutamide monotherapy. All PSA responses were confirmed on repeat measurement. Four patients (5.3%) experienced a greater than ninety percent decline in serum PSA from baseline on study treatment. PSA50 responses were sustained in the majority of cases with median duration of PSA50 response of 21.1 months (95% CI (19.0, 23.2). The median PSA progression-free survival was 3.2 months (95% CI: 3.2, 5.1) in the overall study cohort and 3.2 months (95% CI: 2.8, 6.4) in those with PSA-only progression at study entry. There were no substantial differences with respect to rPFS, composite PFS, or PSA PFS noted between 48- and 96 mg- Dose Expansion cohorts.

Additionally, in a subset of patients (N = 21), there was a transient increase of > 2 ng/mL and 25% above baseline in serum PSA within the first 12 weeks of treatment with subsequent plateau in serum PSA level (Supplementary Figure 2A). Patients with transient PSA increase as defined above appeared to derive sustained clinical benefit with median rPFS of 10.1 months (95% CI: 5.6, 11.7). In contrast, patients whose serum PSA consistently rose beyond the 12 week time point (N = 21) experienced a median rPFS of 7.2 months (95% CI: 3.9, 9.0) (Supplementary Figure 2B).

Predictors of Prolonged Clinical Benefit with ZEN-3694 + Enzalutamide

Exploratory analyses were performed with available genomic and transcriptional data from baseline tumor biopsies to evaluate association with subsequent time to progression on treatment. Interestingly, patients whose baseline metastatic tumor biopsies (N = 13) harbored lower canonical AR transcriptional activity, as assessed by 5-gene score[25] as well as the HALLMARK_ANDROGEN_RESPONSE signature, experienced a longer median time to progression (TTP) (median TTP 19 vs. 45 weeks) (Figure 4A and B). In support of the notion that tumors with lower canonical AR activity might be more responsive to BET inhibition, we observed a trend towards prolonged time to progression amongst patients meeting clinical criteria for aggressive variant prostate cancer (e.g. low serum PSA < 10 ng/mL with concomitant high disease burden (visceral metastases and/or > 10 bone metastases)[26]. The median TTP in patients with aggressive variant disease was 11.6 months (95% CI: 7.2, 12.8) vs. 5.5 months (95% CI: 2.3, 10.6, p = 0.24) in those without aggressive variant clinical features at baseline (Figure 4C).

DISCUSSION

Our results demonstrate that the pan-BET bromodomain inhibitor ZEN-3694 has acceptable tolerability and encouraging preliminary efficacy data in combination with enzalutamide in patients with mCRPC. The median radiographic progression-free survival in the overall cohort was 9 months, and over 10 months in those with prior progression on enzalutamide monotherapy. ZEN-3694 + enzalutamide treatment led to a 2–4 fold reduction in the expression of BET target genes including *MYC*, which was sustained throughout the 24 hour dosing interval. Based on the aggregate of the safety, efficacy, and evidence of robust down-regulation of expression of BET-dependent target genes, ZEN-3694 96 mg daily has been selected as the recommended phase 2 dose to move forward in further clinical development in combination with enzalutamide. The clinical and pharmacodynamic data provide clinical evidence that BET inhibition may be able to abrogate resistance mechanisms and re-sensitize patients to AR-signaling inhibitors.

The prolonged PFS observed in the current study in relevant subsets, including those with radiographic progression at study entry, primary resistance to prior AR targeted therapy, as well as those with prior progression on enzalutamide monotherapy, is consistent with an additive or potentially synergistic interaction between enzalutamide and ZEN-3694. The baseline characteristics of the study cohort are representative of other studies in the post-androgen receptor signaling inhibitor mCRPC setting, including nearly one-third of patients with intermediate or high risk disease by Halabi prognostic model[27], and a quarter of which who required opioid analgesics at study entry. These features argue against the possibility of enrichment of better than average risk group contributing significantly to the prolonged PFS observed on treatment. Taken together, the data support a randomized study to evaluate for the magnitude of benefit of ZEN-3694 in combination with enzalutamide.

With the caveat of cross-trial comparisons, the median PFS observed with ZEN-3694 + enzalutamide in the current study compares favorably to outcomes observed with sequential AR targeting in mCRPC with abiraterone followed by enzalutamide, or vice versa, in prior studies. In the prospective SWITCH phase 2 crossover study, the median PFS of second line enzalutamide and abiraterone were 3.5 and 1.7 months, respectively.[6] Similarly, median progression-free survival with second-line AR targeting therapy have been less than 8 months in most retrospective series.[9] Caution should be applied to over-interpretation of these cross-trial comparisons, and a randomized trial will be necessary to assess the individual contribution of ZEN-3694 added to enzalutamide in mCRPC.

The PSA50 response rate with the combination of ZEN-3694 plus enzalutamide was less than 10% in the study, and median PSA progression-free survival was less than 4 months. Though this may reflect lack of additive benefit of ZEN-3694 in combination with enzalutamide, decline in serum PSA and PSA progression-free survival may not be the best metrics to gauge efficacy of BET bromodomain inhibitors including ZEN-3694. In fact, a subset of patients experienced transient early rises in serum PSA by week 8 of treatment, which were associated with longer time to progression. In addition, tumors harboring lower AR activity at baseline appeared to derive more clinical benefit from treatment. Finally, those with low serum PSA in relation to metastatic disease burden, a clinical profile

consistent with small cell/neuroendocrine prostate cancer, may also have longer radiographic progression-free survival compared to those with higher baseline serum PSA levels. Though these observations are hypothesis-generating and require prospective validation, it raises the intriguing possibility that BET bromodomain inhibitors may restore dependency on AR-signaling in tumors that are less reliant on AR prior to BETi or that BETi is blocking important AR-independent survival mechanisms, such as MYC, which has been shown to be critical for BETi effects in CRPC.[13,28,29] AR-independent mCRPC is becoming more prevalent with the earlier application of AR-signaling inhibitors, and is associated with shortened survival and unmet need to develop novel therapeutic approaches.[30]

The acceptable toxicity profile of ZEN-3694 in combination with enzalutamide stands in contrast to the results observed with several other recent BET inhibitors reported in the literature which have been limited by thrombocytopenia and GI toxicities.[31,32] In the current study, there was substantially less thrombocytopenia observed. Gastrointestinal toxicities were not as prevalent or severe as prior studies and were manageable with early institution of anti-emetics and dose reductions, if necessary. The reasons underlying the potentially more favorable toxicity profile observed in current study, as compared with other BET inhibitors, may relate to patient factors such as excluding prior chemotherapy for mCRPC. Further, it is possible that a pharmacokinetic interaction with ZEN-3694 and enzalutamide may have accelerated production of the first-generation active metabolite ZEN-3791, which may have a more favorable toxicity profile. The differential toxicity compared with other BET inhibitors does not appear to relate to differences in potency, given the robust down-regulation of BETi target genes observed in the current study.

There were several limitations of the study, including the limited number of baseline and on-treatment paired biopsies precluding the ability to identify a consistent predictive biomarker with a high degree of statistical confidence. The non-randomized nature of the dose expansion portion of the study also limits our ability to draw definitive conclusions regarding the potential additive benefit of ZEN-3694, though evidence of contribution is provided by favorable comparison to contemporary controls from other studies as outlined above. AR-V7 splice variant status in circulating tumor cells, a validated resistance mechanism to AR targeted therapy that may be down-regulated with BETi treatment, was not reliably captured in this study in a sufficient number of patients to permit evaluation. Finally, there did not appear to be a relationship between dose level and efficacy outcomes, potentially related to fairly broad inter-patient variability in ZEN-3694 exposure, limited sample size, and limited single agent activity of ZEN-3694.

With the shift in application of potent AR targeted therapy in earlier castration-sensitive settings, there is an increasing medical need to develop therapies that reverse therapeutic resistance and restore dependency on AR signaling. The preliminary data provided by the Phase 1b/2 study of ZEN-3694 plus enzalutamide provides strong justification to further investigate in a prospective, randomized study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

The financial support and study drug supply was provided by Zenith Epigenetics. R.A. received funding from the Prostate Cancer Foundation and the Department of Defense Prostate Cancer Research Program grant W81XWH1820039. W.A. is funded by NIH National Cancer Institute Cancer Center Support Grant (P30CA008748) and Prostate Cancer SPORE (P50CA092629), the Department of Defense Physician Research Award W81XWH-17-1-0124, and the Prostate Cancer Foundation. J.J.A. received funding from grant P50 CA097186. J.J.A is currently employed by the University of Michigan. FYF received funding from the Prostate Cancer Foundation.

REFERENCES

1. Siegel RL, Miller KD, and Jemal A. Cancer statistics, 2020. CA: A Cancer Journal for Clinicians 2020;70(1):7–30. [PubMed: 31912902]
2. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 2013; 368:138–48. [PubMed: 23228172]
3. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014; 371: 424–33. [PubMed: 24881730]
4. Fizazi K, Tran N, Fein L, et al. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial. Lancet Oncology 2019;20:686–70. [PubMed: 30987939]
5. Chi KN, Agarwal N, Anders B, et al. Apalutamide for metastatic castation-sensitive prostate cancer. New Engl J Med 2019:381:13–24. [PubMed: 31150574]
6. Khalaf DJ, Annala M, Taavitsainen S, et al. Optimal sequencing of enzalutamide and abiraterone acetate plus prednisone in metastatic castration-resistant prostate cancer: a multicentre, randomised, open-label, phase 2, crossover trial. Lancet Oncology 2019;20:1730–39. [PubMed: 31727538]
7. Attard G, Borre M, Gurney H, et al. Abiraterone alone or in combination with enzalutamide in metastatic castration-resistant prostate cancer with rising prostate-specific antigen during enzalutamide treatment. J Clin Oncol 2018;36:2639–46. [PubMed: 30028657]
8. de Bono JS, Chowdhury S, Feyerabend S, et al. Antitumour activity and safety of enzalutamide in patients with metastatic castration-resistant prostate cancer previously treated with abiraterone acetate plus prednisone for ≥ 24 weeks in Europe. European Urology 2018;74:37–45. [PubMed: 28844372]
9. Mori K, Miura N, Mostafaei H, et al. Sequential therapy of abiraterone and enzalutamide in castration-resistant prostate cancer: a systematic review and meta-analysis. Prostate Cancer and Prostatic Diseases 2020 [published online 09 March 2020].
10. Morris MJ, Heller G, Bryce AH, et al. Alliance A031201: a phase III trial of enzalutamide versus enzalutamide, abiraterone, and prednisone for metastatic castration resistant prostate cancer. J Clin Oncol 2019;37, no. 15_suppl (May 20, 2019) 5008.
11. Antonarakis ES, Lu C, Wang H, et al. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. N Engl J Med 2014;371:1028–1038. [PubMed: 25184630]
12. Montgomery RB, Mostaghel EA, Vessella R, et al. Maintenance of intratumoral androgens in metastatic prostate cancer: a mechanism for castration-resistant tumor growth. Cancer Res 2008;68:4447–54. [PubMed: 18519708]
13. Quigley DA, Dang HX, Zhao SG, et al. Genomic Hallmarks and Structural Variation in Metastatic Prostate Cancer. Cell 2018;175:889. [PubMed: 30340047]
14. Aggarwal R, Huang J, Alumkal JJ, et al. Clinical and Genomic Characterization of Treatment-Emergent Small-Cell Neuroendocrine Prostate Cancer: A Multi-institutional Prospective Study. J Clin Oncol 2018;36:2492–2503. [PubMed: 29985747]
15. Arora VK, Schenkein E, Murali R, et al. Glucocorticoid receptor confers resistance to antiandrogens by bypassing androgen receptor blockade. Cell 2013;155:1309–22. [PubMed: 24315100]

16. Shah N, Wang P, Wongvipat J, et al. Regulation of the glucocorticoid receptor via a BET-dependent enhancer drives antiandrogen resistance in prostate cancer. Elife 2017;6:e27861. [PubMed: 28891793]
17. Mertz JA, Conery AR, Bryant BM, et al. Targeting MYC dependence in cancer by inhibiting BET bromodomains. PNAS 2011;108:16669–74. [PubMed: 21949397]
18. Attwell S, Jahagirdar R, Norek K, et al. Preclinical characterization of ZEN-3694, a novel BET bromodomain inhibitor entering phase I studies for metastatic castration-resistant prostate cancer (mCRPC) In CANCER RESEARCH 2016; (Vol. 76). 615 CHESTNUT ST, 17TH FLOOR, PHILADELPHIA, PA 19106–4404 USA: AMER ASSOC CANCER RESEARCH.
19. Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 2008; 26:1148–59. [PubMed: 18309951]
20. Tsujikawa L, Norek K, Calosing C, et al. Abstract LB-038: Preclinical development and clinical validation of a whole blood pharmacodynamic marker assay for the BET bromodomain inhibitor ZEN-3694 in metastatic castration-resistant prostate cancer patients. Cancer Research 2017;77, Issue 13 Supplement, pp. LB–038.
21. The Molecular Signatures Database v7.0 (Broad Institute).
22. Liu P, Ramachandran S, Ali Seyed M, et al. Sex-determining region Y box 4 is a transforming oncogene in human prostate cancer cells. Cancer research 2006;66(8):4011–19. [PubMed: 16618720]
23. Wyce A, Degenhardt Y, Bai Y, et al. Inhibition of BET bromodomain proteins as a therapeutic approach in prostate cancer. Oncotarget 2013;4:2419–29. [PubMed: 24293458]
24. Aggarwal R, Abida W, Schweizer M, et al. CTo95: A phase Ib/IIa study of the BET bromodomain inhibitor ZEN-3694 in combination with enzalutamide in patients with metastatic castration-resistant prostate cancer (mCRPC). In Proceedings of the AACR Meeting; 2019.
25. Miao L, Yang L, Li R, Rodrigues DN, Crespo M, Hsieh JT, … Raj GV (2017). Disrupting Androgen Receptor Signaling Induces Snail-Mediated Epithelial-Mesenchymal Plasticity in Prostate Cancer. Cancer research, 77(11), 3101–3112. [PubMed: 28302679]
26. Corn PG, Heath EI, Zurita A, et al. Cabazitaxel plus carboplatin for the treatment of men with metastatic castration-resistant prostate cancers: a randomised, open-label, phase 1–2 trial. Lancet Oncol 2019;20(10):1432–43. [PubMed: 31515154]
27. Halabi S, Lin C, Kelly WK, et al. Updated prognostic model for predicting overall survival in first-line chemotherapy for patients with metastatic castration-resistant prostate cancer. J Clin Oncol 2014;32:671–77. [PubMed: 24449231]
28. Coleman DJ, Gao L, Schwartzman J, et al. Maintenance of MYC expression promotes do novo resistance to BET bromodomain inhibition in castration-resistant prostate cancer. Science Reports 2019;9:3823.
29. Coleman DJ, Gao L, King CJ, et al. BET bromodomain inhibition blocks the function of a critical AR-independent master regulatory network in lethal prostate cancer. Oncogene 2019;38:5658–69. [PubMed: 30996246]
30. Aggarwal R, Huang J, Alumkal JJ, et al. Clinical and genomic characterization of treatment-emergent small cell neuroendocrine prostate cancer: a multi-institutional prospective study. J Clin Oncol 2018;36:2942–2503.
31. Piha-Paul S, Hann CL, French CA, et al. Phase 1 study of molibresib (GSK525762), a bromodomain and extra-terminal domain protein inhibitor, in NUT carcinoma and other solid tumors. JNCI Cancer Spectrum [published online 06 November 2019].
32. Patel MR, Garcia-Manero G, Paquette R, et al. Phase 1 dose escalation and expansion study to determine safety, tolerability, pharmacokinetics, and pharmacodynamics of the BET inhibitor FT-1101 as a single agent in patients with relapsed or refractory hematologic malignancies. Blood, 2019;134(suppl 1):3907.

Statement of Translational Relevance

BET bromodomain inhibitors (BETi) demonstrate *in vivo* activity in enzalutamide-resistant prostate cancer models via down-regulation of bypass signaling pathways including MYC. Clinical translation of BETi as a therapeutic strategy in metastatic castration resistant prostate cancer (mCRPC) has heretofore been limited by significant toxicity including risk of thrombocytopenia. In the current phase 1a/2b study of the pan-BETi ZEN-3694 in combination with enzalutamide in 75 patients with abiraterone and/or enzalutamide-resistant mCRPC, the combination was well tolerated without reaching a maximally tolerated dose. Less than 5% of patients experienced a grade ≥ 3 thrombocytopenia. Robust, dose-dependent, and sustained down-regulation of expression of BET inhibitor target genes including MYC was observed using a whole blood RNA assay. Encouraging efficacy was observed including a median radiographic progression-free survival of over 10 months in those with prior progression on enzalutamide monotherapy. Clinical benefit was particularly pronounced in high-risk subgroups including those with an aggressive variant clinical phenotype as well as those with lower androgen receptor (AR) transcriptional activity in baseline tumor biopsies. A randomized study is planned with ZEN-3694 at the recommended phase 2 dose of 96 mg orally once daily in combination with enzalutamide in mCRPC with prior progression on enzalutamide or abiraterone.

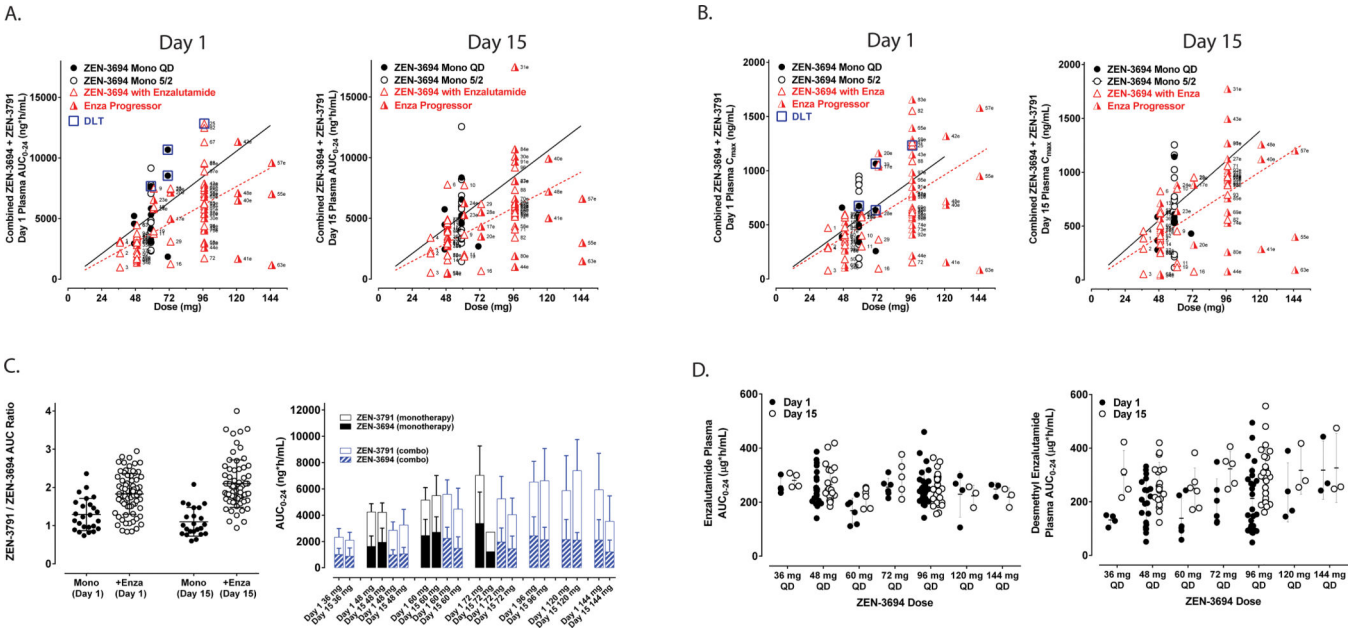


Figure 1. Pharmacokinetic analyses.

A and B. Area-under-the-curve (AUC) from 0 to 24 hours ($AUC_{0–24}$) and maximum serum concentration, respectively, of ZEN-3694 + ZEN-3791 (first generation active metabolite) serum concentration on day 1 and day 15 of cycle 1 (red triangles). Overlaid $AUC_{0–24}$ data from the monotherapy trial of ZEN-3694[23] are shown for dose levels 48 and 72 mg daily (black circles). **C.** Ratio of ZEN-3791 (first generation active metabolite) vs. ZEN-3694 (parent compound) from the prior monotherapy trial[23] and in combination with enzalutamide on day 1 and day 15 of cycle 1. **D.** Steady-state serum concentration of enzalutamide and desmethylenzalutamide following 14 day lead-in of enzalutamide (day −14 to day −1), by ZEN-3694 dose level.

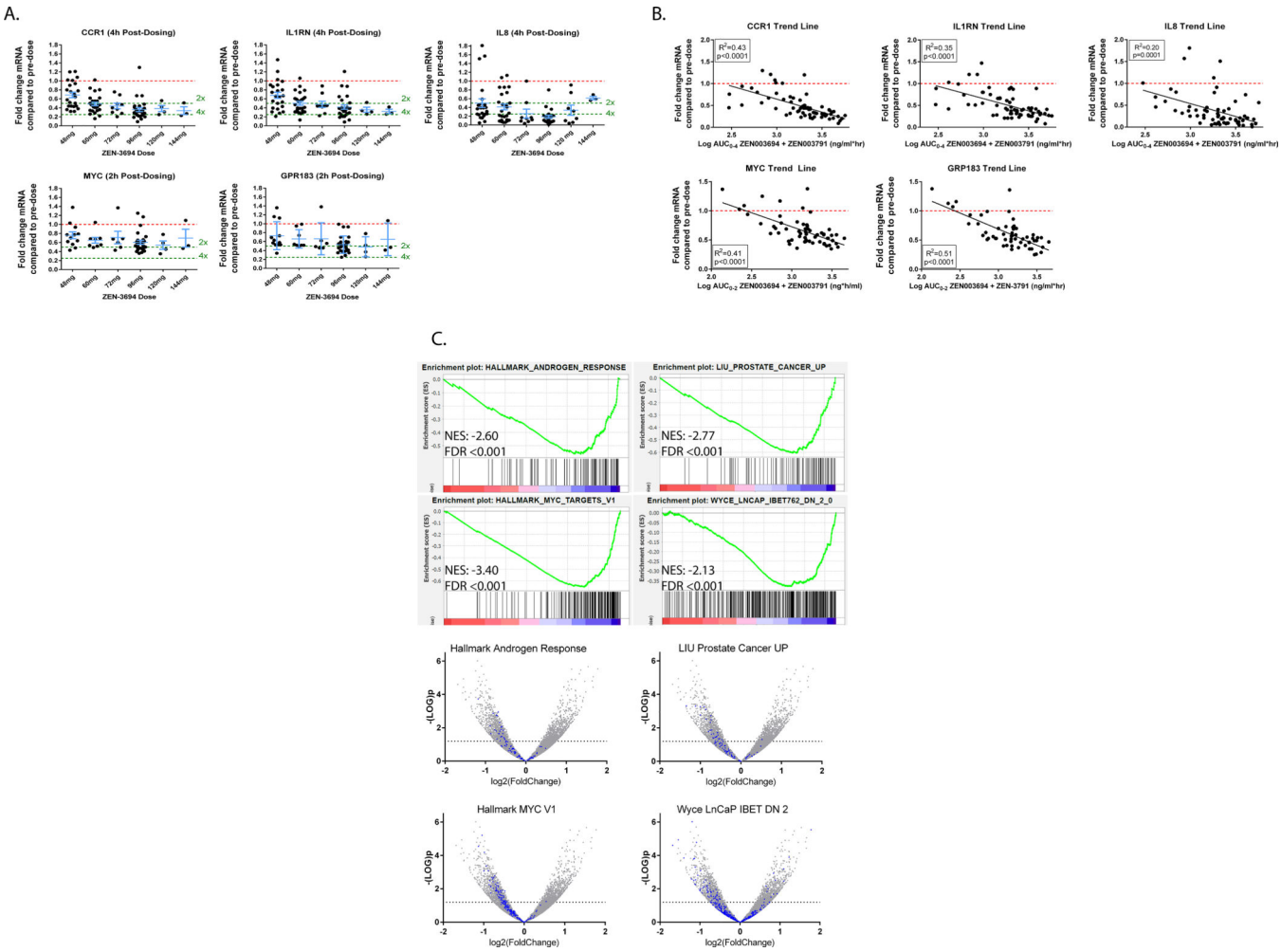


Figure 2. Pharmacodynamic assessments.

A. Fold-change from baseline in whole blood RNA expression of BET inhibitor target genes *CCR1*, *IL1RN*, *IL-8*, *MYC,* and *GPR183* by ZEN-3694 dose level. **B.** Correlation between fold change from baseline in whole blood RNA expression of BET inhibitor target genes with $AUC_{0–24}$ of ZEN-3694 + ZEN-3791 indicates strong PK-PD relationship. **C.** Gene set enrichment analysis of change from baseline in gene expression by RNA-Seq in paired metastatic tumor biopsies. Down-regulation of MYC signaling pathway is observed in on-treatment versus baseline tumor biopsy.

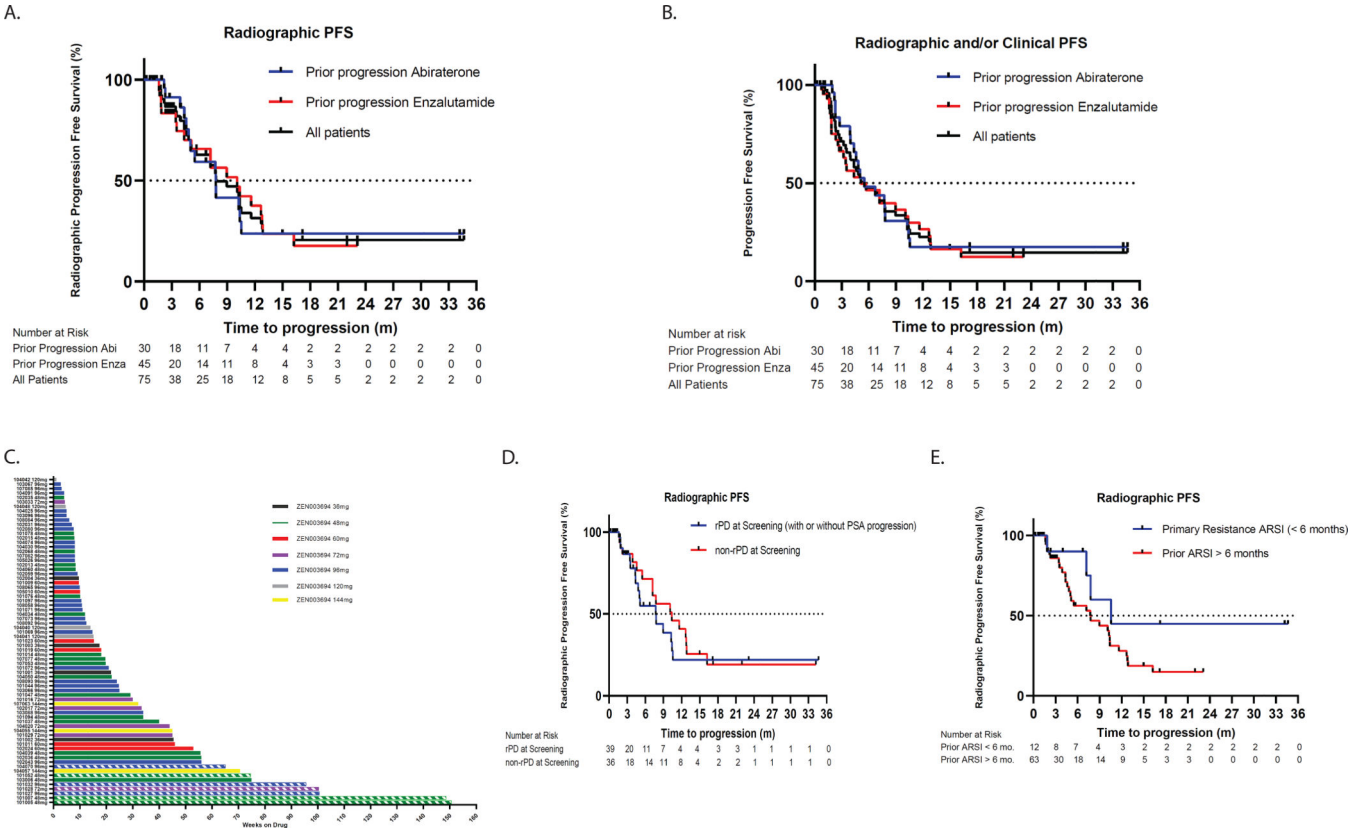


Figure 3. Radiographic progression-free survival and duration of treatment.

A. Kaplan-Meier curve demonstrating radiographic progression-free survival by PCWG2 criteria in all evaluable study participants (black curve), patients with prior enzalutamide progression (blue curve), or prior abiraterone progression (green curve). **B.** Kaplan-Meier curve demonstrating composite progression-free survival (time to first clinical or radiographic progression) in **C.** Swimmer's plot showing duration of treatment, with color labels by ZEN-3694 dose level (hashed line = treatment ongoing). **D and E.** Kaplan-Meier curves showing radiographic progression-free survival in subsets of patients with radiographic progression or primary resistance to prior androgen signaling inhibitor, respectively.

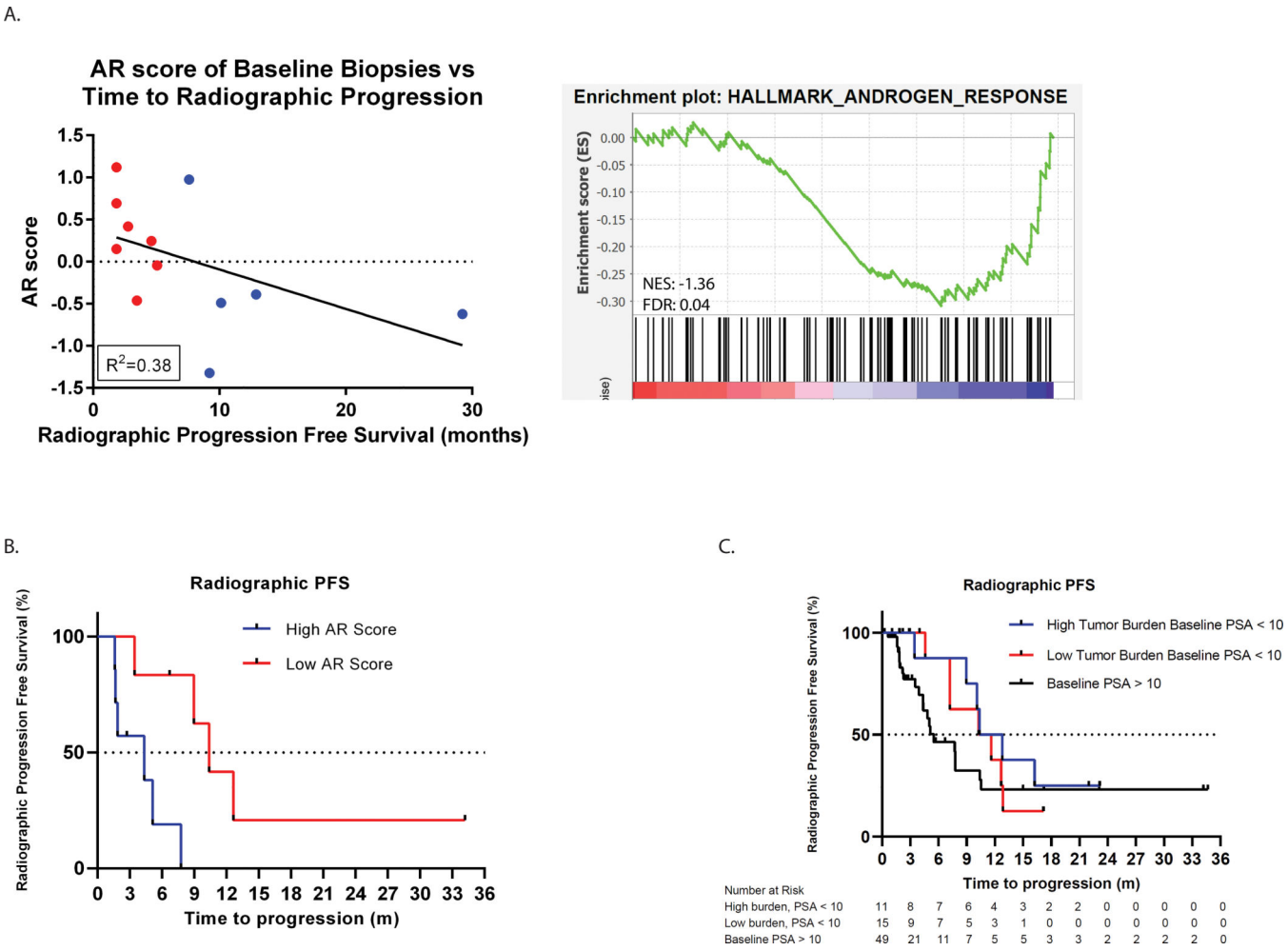


Figure 4. AR signaling score and clinical outcomes

A. Lower AR activity level in baseline tumor biopsies is correlated with longer time on study (R^2=0.38) using either the 5-gene AR score (left) or the HALLMARK_ANDROGEN_RESPONSE (right) signatures. For the hallmark signature, baseline gene expression of biopsies from patients with radiographic progression prior to 24 weeks vs. greater than 24 weeks were compared (FDR = 0.04). **B.** Kaplan-Meier curve showing significant increase in time to median radiographic progression free survival in patients with lower AR signaling compared to patients with higher AR signaling score (median rPFS 10.4 months in tumors with low AR score vs. 4.3 months in tumors with high AR activity). **C.** Patients with high tumor burden and lower baseline PSA levels (< 10 ng/mL) (blue curve) demonstrate longer PFS than patients with higher baseline PSA (> 10 ng/mL) levels.

Table 1:

Baseline Characteristics

		Study Cohort (n=75)*
Median age (range), years		70 (47–89)
ECOG score		
0		42 (56%)
1		33 (44%)
Opioid analgesic use		18 (24%)
Visceral metastases at study entry (%)		21 (28%)
Median PSA, ng/mL (range)		26.99 (0.15 – 1701.8)
Median ALP, U/L (range)		82 (33 – 487)
Median LDH, U/L (range)		188 (98 – 543)
Median Hemoglobin, g/dL (range)		13.2 (6.4 – 20.2)
Halabi risk category[24]		
	Low	50 (67)
	Intermediate	16 (21)
	High	8 (11)
	Unknown	1 (1)
Prior number of systemic cancer treatments (range)		3 (1–7)
Prior resistance to AR targeted therapy (%)		
	Abiraterone	30 (40)
	Enzalutamide	34 (45)
	Both	11 (15)
Duration of prior AR targeted therapy (range), months		14.3 (1.0–58.3)
Reason for prior abiraterone or enzalutamide discontinuation		
	Radiographic progression	8 (11%)
	Radiographic and PSA progression	31 (41%)
	Clinical and PSA progression	3 (4%)
	PSA progression	33 (44%)
	Clinical progression	0

ALP, alkaline phosphatase; AR, androgen receptor; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PSA, prostate-specific antigen.

*For data recorded in the clinical database as of the data cutoff date of 07 January 2020.

Table 2.

Summary of All Grades Treatment-related Adverse Events by Dose Level of ZEN-3694

	36mg QD n=4	48 mg QD n=21	6Dmg QD n=6	72mg QD n=6	96mg QD n=31	120mg QD N=4	144mg QD N=3	TOTAL n=75 (%)
Blood creatinine Increased			2		3			5 (6.7)
Constipation		1			3			4 (5.3)
Decreased Appetite		2	2	1	10	3	2	20 (26.7)
Diarrhea				1	5			6(8)
Dizziness				1	3			4 (5.3)
Dysgeusia		2	0	0	10	1	3	16 (21.3)
Dyspepsia		1			2			3(4)
Fatigue	1	8	1	2	13	3	1	29 (38.7)
Nasal congestion					3			3(4)
Nausea		7	2	3	17	3	2	34 (45.3)
Photopsia		1			3			4 (5.3)
Photosensitivity		2			3			5 (6.7)
Rash					3			3(4)
Rash maculopapular		3			1		1	5 (6.7)
Taste disorder			1	1	3			5 (6.7)
Thrombocytopenia		1	1	2	6		1	11 (14.7)
Vision blurred					2	1		3(4)
Visual symptoms	3	12	4	6	17	4	2	48 (64)
Vomiting		1			3	1		5 (6.7)
Weight loss & Abnormal WL	1			1	3	1	2	8(10.7)

[A]Visual symptoms defined as a transitory perception of bright lights and/or light flashes with or without visual color tinges

Practical Considerations and Challenges for Germline Genetic Testing in Patients With Prostate Cancer: Recommendations From the Germline Genetics Working Group of the PCCTC

Brittany M. Szymaniak, PhD[1]; Lauren A. Facchini, MS[2]; Veda N. Giri, MD[3]; Emmanuel S. Antonarakis, MD[4]; Tomasz M. Beer, MD[5]; Maria I. Carlo, MD[6]; Daniel C. Danila, MD[6]; Mallika Dhawan, MD[7]; Daniel George, MD[8]; Julie N. Graff, MD[9]; Shilpa Gupta, MD[10]; Elisabeth Heath, MD[11]; Celestia S. Higano, MD[12]; Glenn Liu, MD[13]; Ana M. Molina, MD[14]; Channing J. Paller, MD[4]; Akash Patnaik, MD, PhD, MMSc[15]; Daniel P. Petrylak, MD[16]; Zachery Reichert, MD, PhD[17]; Matthew B. Rettig, MD[18]; Charles J. Ryan, MD[10]; Mary-Ellen Taplin, MD[19]; Jake Vinson, BSc[20]; Young E. Whang, MD, PhD[21]; Alicia K. Morgans, MD, MPH[22]; Heather H. Cheng, MD, PhD[12]; and Rana R. McKay, MD[23]

abstract

Germline genetic testing is now routinely recommended for patients with prostate cancer (PCa) because of expanded guidelines and options for targeted treatments. However, integrating genetic testing into oncology and urology clinical workflows remains a challenge because of the increased number of patients with PCa requiring testing and the limited access to genetics providers. This suggests a critical unmet need for genetic services outside of historical models. This review addresses current guidelines, considerations, and challenges for PCa genetic testing and offers a practical guide for genetic counseling and testing delivery, with solutions to help address potential barriers and challenges for both providers and patients. As genetic and genomic testing become integral to PCa care, developing standardized systems for implementation in the clinic is essential for delivering precision oncology to patients with PCa and realizing the full scope and impact of genetic testing.

JCO Oncol Pract 16:811-819. © 2020 by American Society of Clinical Oncology

INTRODUCTION

Genomics is rapidly pushing oncology closer to an actualized version of precision medicine.[1,2] In the era of poly (ADP-ribose) polymerase inhibition and immunotherapy, genetic testing may yield information that will affect therapeutic choices, in addition to informing the patient about personal and familial risk.[3-5] Multiple guidelines now include germline genetic testing for men with prostate cancer (PCa), although incorporating testing into clinical workflows remains a challenge.[5,6] This article addresses (1) current guidelines for germline testing, (2) key aspects of testing and counseling, (3) a road map for genetic testing and counseling delivery, (4) challenges of testing and possible solutions, and (5) benefits and limitations of testing.

Germline Genetic Counseling for Men With PCa

Since the landmark article by Pritchard et al[7] that described a relatively high prevalence of germline mutations in DNA repair genes in men with metastatic PCa, other groups have reported the prevalence of germline mutations in PCa ranging between 7.5% and 19%, with *BRCA2* being the highest overall contributor.[8-11] Consequently, several groups issued recommendations for germline testing (Table 1), which place significant demands on clinical workflows and resources for genetic counseling. Genetic counselors (GCs) are trained to assess family histories for genetic risk, provide pretest and post-test counseling, order appropriate testing, and interpret test results. Unfortunately, access to genetic providers is limited, with the majority of the small workforce usually centered in urban areas and academic institutions.[12,13] In 2016, the Genetic Counselor Workforce Working Group estimated a growth of 72% in the workforce between 2017 and 2026, with demand not expected to meet population equilibrium until 2024-2030.[14] This limited access may necessitate other health care providers, including oncologists, urologists, and primary care physicians, to absorb some responsibility for genetic testing. However, these providers may be insufficiently trained in genetics, resulting in inappropriate testing and misinformation.[15-17]

The increased number of men with PCa to be tested and the scarcity of GCs suggest a critical unmet need for expanded genetic services through novel approaches outside of historic delivery models.[18] Evolving service models that incorporate phone and video telemedicine can be particularly useful when geography or public health crises, such as COVID-19, make in-person visits challenging.[19,20] Hybrid service models

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on July 29, 2020 and published at ascopubs.org/journal/op on September 28, 2020: DOI https://doi.org/10.1200/OP.20.00431

that divide responsibilities between physicians and GCs are also options.[21] Collaboration between GCs and clinicians is critical to determine which approach best suits a practice, because there is no one-size-fits-all solution.

Delivery of Germline Testing and Counseling

Initiating genetic testing. One of the greatest hurdles is ensuring that appropriate patients are systematically identified for testing. Developing a plan to consistently screen and identify patients based on current guidelines is necessary (Table 1). Assigning screening to a team member or using patient-completed family history questionnaires can facilitate referral and testing processes. Automated electronic medical record (EMR) features can trigger genetic counseling referrals or alert the clinical team based on a diagnosis code for metastatic PCa or family history/pedigree functionality.

After patients are identified, several options for counseling and testing are available:

1. Referral to a geneticist or GC for in-person, telephone-based, or telemedicine counseling services in response to manual referral or automated EMR triggers.
2. Treating clinicians perform pretest consent and order germline genetic testing directly: If genetic counseling services are unavailable, testing is urgent, or workflow supports providers initiating testing, treating providers can perform pretest education, obtain informed consent, and order genetic testing.[21] Providers should consider any clinical, psychosocial, and financial issues when determining whether to pursue testing within their practice or refer to a remote/telehealth genetic service if they do not have access within the practice.
3. Patient-initiated testing (PIT) platforms: Some commercial genetic testing laboratories, such as Color and Invitae, offer clinical-grade testing that can be initiated by the patient. This process may involve a pretest clinician review and the option for post-test genetic counseling. However, there remain concerns about guidance on test selection, limitations in genetic counseling, lack of follow-up regarding future reclassification of variants, potential for misinterpretation of results, and propagation of misinformation within families. Furthermore, PIT may not include genes important to a patient's personal or family history, potentially creating a false sense of reassurance if testing is negative. Given this, provider-initiated testing is preferred.
4. Direct-to-consumer (DTC) testing platforms: DTC genetic testing has become increasingly popular, likely because of easy access and no medical provider oversight. DTC testing is not comprehensive and should not be considered a substitute for clinical-grade testing. Although 23&Me has Food and Drug Administration approval to report on the three known Ashkenazi Jewish BRCA1/2 founder variants, the National Comprehensive Cancer Network (NCCN) cautions that any results should be confirmed with a clinical-grade test.[22] Providers should be skeptical of any raw data findings from secondary companies, such as Promethease, which are prone to false positives and false negatives.[23]

Family cancer history intake. Although all patients with high-risk localized or metastatic PCa should undergo germline genetic testing regardless of family history, accurately evaluating a patient's personal and family history is essential to determine whether patients need a broader germline panel. Furthermore, gathering a family history can help inform personal and family screening recommendations in the event of negative testing. Cancer counseling sessions include a three- to four-generation pedigree with information on maternal and paternal relatives with cancer, age of diagnosis, age/cause of death, and any prior genetic testing.[22,24] For relatives with PCa, the Gleason grade, metastatic status, and/or cause of death can be useful. Information about ancestry (eg, Ashkenazi Jewish) and consanguinity should be noted. Family history questionnaires can be completed in the clinic or electronically.

Complete family histories ensure that the most informative, cost-effective testing is performed. Although the presence of other cancer types in a family history may be explained by a mutation in a PCa predisposition gene, providers should consider expanded testing for genes related to the observed cancers in a family history when necessary. For instance, hereditary pancreatic cancer and PCa typically occur in the setting of a pathogenic *BRCA2* variant. However, it may be reasonable to include other genes associated with pancreatic cancer, such as *CDKN2A* and *CDK4*.

Somatic next-generation sequencing. Somatic next-generation sequencing tumor testing is increasingly used to guide treatment decision making and can be performed in parallel with germline testing. In addition to detecting tumor-specific mutations, it can sometimes identify potential germline mutations. Most somatic testing platforms are not validated to distinguish germline from somatic-only mutations, even if paired testing with a blood or saliva sample is performed. Thus, a referral to genetics is recommended to determine whether confirmatory or more comprehensive testing is warranted. Providers should consider the variant allele frequency, actionability of the gene, classification of the variant, and tumor type when reviewing somatic variants for possible germline origin.[25]

Pretest education and informed consent. Pretest education and informed consent discussions should review the purpose of testing; general information about included genes; possible test results (Table 2); medical management implications; review of possible benefits, risks, and limitations (Table 3); and the voluntary nature of testing.[24,26] Several major medical societies have also published detailed guidelines reviewing the components of pretest counseling and informed consent to help clinicians.[24] Clinical teams

TABLE 1. Summary of the Current PCa Genetic Testing Guidelines

Organization	Source	Guidelines	Genes
National Comprehensive Cancer Network	Genetic/familial high-risk assessment: breast, ovarian, and pancreatic version 1.2020[22]	Testing is clinically indicated in the follow scenarios:	*ATM* *BARD1*[a] *BRCA1* *BRCA2* *BRIP1* *CDH1*[a] *CDKN2A*[a] *CHEK2* *MSH2* *MLH1* *MSH6* *PMS2* *EPCAM* *NBN* *NF1*[a] *PALB2* *PTEN*[a] *RAD51C* *RAD51D* *STK11*[a] *TP53*
	Hereditary cancer testing criteria	1. Individuals with any blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene	
		2. Individuals meet the criteria below but with previous limited testing (eg, single gene and/or absent deletion duplication analysis) interested in pursuing multigene testing	
		3. Personal history of cancer	
		• Metastatic or intraductal PCa at any age	
		• High-grade (Gleason score ≥ 7) PCa with:	
		o Ashkenazi Jewish ancestry; or	
		o ≥ 1 close relative with breast cancer at age ≤ 50 years or ovarian, pancreatic, or metastatic or intraductal PCa at any age; or	
		o ≥ 2 close relatives with breast or PCa (any grade) at any age	
		• A mutation identified on tumor genomic testing that has clinical implications if also identified in the germline	
		• To aid in systemic therapy decision making	
		4. Family history of cancer	
		• An affected or unaffected individual with a first- or second-degree blood relative meeting any of the criteria listed above (except individuals who meet criteria only for systemic therapy decision making)	
		There is a low probability (< 2.5%) that testing will have findings of documented clinical utility in the following scenarios:	
		• Men diagnosed with localized PCa with Gleason score < 7 and no close relative with breast, ovarian, pancreatic, or PCa	
National Comprehensive Cancer Network	Prostate cancer, version 1.2020[44]	Germline testing is recommended for patients with PCa and any of the following:	*ATM* *BRCA1* *BRCA2* *CHEK2* *HOXB13* *MLH1* *MSH2* *MSH6* *PALB2* *PMS2*
		• High-risk, very-high-risk, regional, or metastatic PCa	
		• Ashkenazi Jewish ancestry	
		• Family history of high-risk germline mutations (eg, *BRCA1/2*, Lynch mutation)	
		• A positive family history of cancer:	
		o A strong family history of PCa consists of: brother or father or multiple family members who were diagnosed with PCa (but not clinically localized Grade Group 1) at < 60 years of age or who died from PCa; OR	
		o ≥ 3 cancers on same side of family, especially diagnoses ≤ 50 years of age: bile duct, breast, colorectal, endometrial, gastric, kidney, melanoma, ovarian, pancreatic, prostate (but not clinically localized Grade Group 1), small bowel, or urothelial cancer	

(continued on following page)

TABLE 1. Summary of the Current PCa Genetic Testing Guidelines (continued)

Organization	Source	Guidelines	Genes
Expert Panel	Philadelphia Consensus meeting publication, 2017[45]	Men meeting any one of the following suggested criteria should undergo genetic counseling and genetic testing: • All men with PCa from families meeting established testing or syndromic criteria for the following: o HBOC (Consensus: 93%) o HPC (Consensus: 95%) o LS (Consensus: 88%) • Men with PCa with two or more close blood relatives on the same side of the family with a cancer in the following syndromes: o Post-consensus discussion included consideration of age cutoff for this criterion. A specific age cutoff will require additional data, and age at diagnosis is important to inquire about in the genetic counseling session with patients. ■ HBOC (Consensus: 93%) ■ HPC (Consensus: 86%) ■ LS (Consensus: 86%) • All men with metastatic castrate-resistant PCa should consider genetic testing (Consensus: 67%). Post-consensus discussion also included consideration of testing men with metastatic, hormone-sensitive PCa to identify germline mutations to inform potential future treatment options and cascade testing in families. Men with tumor sequencing showing mutations in cancer-risk genes should be recommended for germline testing, particularly after factoring in additional personal and family history (Consensus: 77%).	*ATM* *BRCA1* *BRCA2* *HOXB13* *MSH2* *MLH1* *PMS2* *MSH6*
AUA	Clinically localized PCa: AUA/ASTRO/SUO guideline, 2017[46]	The Panel recommends that clinicians take a detailed family history of cancers and give consideration to patient referral for genetic screening and counseling for men with localized high-risk PCa, particularly in the setting of family history of first-degree relatives with cancers of breast, ovary, pancreas, other GI cancers, and lymphoma.	No genes specified for germline testing

Abbreviations: ASTRO, American Society of Therapeutic Radiation and Oncology; AUA, American Urological Association; HBOC, hereditary breast and ovarian cancer syndrome; HPC, hereditary prostate cancer; LS, Lynch syndrome; PCa, prostate cancer; SUO, Society of Urologic Oncology.
[a]These genes are not currently associated with PCa.

should note the requirements for documentation of informed consent, which differ by state and institutional policies.

Test selection and ordering. Many commercial laboratories offer clinical genetic testing for hereditary cancer syndromes. Testing panels range from targeted, guidelines-based panels to comprehensive, pan-cancer panels that may include preliminary evidence genes. Some major laboratories, such as Ambry Genetics, Invitae, and GeneDx, offer PCa-specific panels that include the following genes: *ATM, BRCA1, BRCA2, CHEK2, HOXB13, MLH1, MSH2, MSH6, NBN, PALB2, PMS2,* and *TP53*. Genetic testing panels are subject to change, and decisions regarding specific genetic tests should be individualized based on

TABLE 2. Possible Genetic Test Results[47,48]

Interpretation	Result	Definition
Positive	Pathogenic	An alteration in the DNA that is associated with increased disease risk.
	Likely pathogenic	An alteration in the DNA that is likely to be associated with increased disease risk. Meets most but not all criteria to be classified as pathogenic.
Uncertain	Variant of uncertain significance	An alteration in the DNA that may or may not be disease causing. Insufficient evidence to classify as either pathogenic or benign.
Negative	Likely benign	An alteration in the DNA that is unlikely to be associated with increased disease risk. Meets most but not all criteria to be classified as benign.
	Benign	An alteration in the DNA that is not associated with increased disease risk.

TABLE 3. Pretest Talking Points Regarding the Benefits and Risks/Limitations of Genetic Testing[27,49]

Benefits	Risks/Limitations
May help explain personal cancer history	May increase anxiety and guilt regarding hereditary cancer risk
May help inform prognosis	Potential for uncertain results: 1) Variants of uncertain significance, or 2) Positive results in lesser established genes and those with no management guidelines currently available
May help inform risks for additional cancers	Genetic discrimination risks (life insurance or long-term care insurance)
May help guide treatment decisions	Financial barriers
May help inform cancer risks for family members	

factors such as laboratory reputation and quality, insurance networks, genes offered and customizability of panels, laboratory billing practices, follow-up testing options for family members, turnaround times, and availability of genetic counseling services.

Clinicians should recognize that larger panels increase the probability of detecting variants of uncertain significance (VUS), incidental/secondary findings (pathogenic variants in genes not related to hereditary PCa), and variants associated with syndromes that may be outside of the scope of clinicians treating PCa (Tables 2 and 3). Clinical workflows must ensure that tasks involved with ordering genetic testing include determination of insurance coverage and submission of orders, standardized collection and shipment of samples, and a clear chain of responsibility.

Insurance coverage for germline testing is in flux. Although the cost of genetic testing has decreased, the possible out-of-pocket (OOP) cost for patients can be difficult to discern because of the varying billing policies of laboratories and insurance coverages.[27] Although the NCCN hereditary breast and ovarian cancer guidelines (v3.2019) are often the primary source used by payers, including Medicare, to develop coverage policies, most have their own criteria that determine testing coverage. These criteria may not be up to date with current NCCN guidelines, potentially excluding PCa from their criteria completely, and may mandate a consultation with certified GC for approval.

Many, but not all, laboratories work with commercial insurance companies to negotiate coverage into their policies and will provide an estimate of the OOP cost of testing. Not all insurance companies require prior authorization for genetic testing. Laboratory online ordering portals will often indicate whether provider-initiated insurance prior authorization is needed. Typically, all components of the billing process, including submission of insurance prior authorization, are handled by the laboratory. Several commercial laboratories offer a patient-pay or fixed OOP cost, often $250 or lower, making testing more financially accessible. In addition, patients may qualify for a sponsored testing program at no cost in exchange for de-identified data shared with the sponsoring companies.

Results delivery and follow-up. Methods for delivering test results vary, depending on workflow, availability of genetic counseling services, and provider comfort level and training. Regardless of result type, genetic test reports should be offered to patients for their own records and uploaded into the EMR. Refer to Table 2 for information regarding the following result types. Options for returning results include:

1. Ordering provider refers all patients for post-test counseling, either through referral to a local GC or a telehealth genetic counseling service.
2. Ordering provider refers patients with complex results (eg, positive and/or VUS) for post-test counseling. This type of blended approach to genetic testing has been previously discussed and has received strong consensus across multiple disciplines.[21,26]
   a) Negative results: Clinical teams can disclose results via telephone, patient portal message, a follow-up appointment, or a letter summarizing the results and providing contact information if there are questions. A templated letter can be generated with GC input. Cancer screening recommendations should be based on the family history and should be reviewed with the patient. For example, men with a first-degree relative with PCa remain at increased risk for PCa and should initiate prostate screening at a younger age per routine guidelines. Patients should be encouraged to discuss updates to personal and family history, which may prompt consideration of additional genetic testing or altered screening recommendations.
3. Ordering provider discloses all result types. It is important to note that even in this situation, a referral can be made to genetics for post-test counseling.
   a) Positive results: Providers should discuss and document the implications of the results in terms of cancer risks associated with the identified gene mutation, additional cancer screening recommendations, appropriate referrals, and possible implications for treatment. Providers should also recommend cascade testing, which entails genetic counseling and testing in at-risk relatives of

individuals identified to carry specific genetic mutations or further testing in the family based on family history. Access to the proband's test report will be essential for family members considering testing.

b) VUS results: It is critical to review the uncertainty of whether the specific gene mutation identified is disease causing or a benign variation. The vast majority of VUS results are later reclassified to negative[28,29]; thus, they are typically treated as negatives, and screening recommendations are made based on personal and family history. Testing family members for a VUS is typically not recommended unless it is in the context of a variant resolution or research program. When a VUS is reclassified, new reports are customarily issued to the ordering provider, and it is therefore the responsibility of the ordering provider to follow up with patients over the long term concerning any reclassifications. Patients should be encouraged to check in with their providers every few years to see whether there are updates to the classification. It is also important to note the possibility of discrepant variant classifications across laboratories. These discrepancies may cause difficulty determining how to appropriately manage patients and family members. ClinVar is a free, publicly available database that aggregates variant classifications, although a limitation is that entry submissions may not be completely up to date.

Cascade testing. The concept of cascade testing should be introduced as part of pretest counseling. Family letters can facilitate genetic testing for other relatives in the event of a positive result and typically include a short description of the cancer syndrome, the specific mutation identified, information on how to contact a GC in their area, and laboratory/specimen identification for the patient's testing. A number of the genes associated with hereditary PCa, such as *BRCA1/2* and the mismatch repair genes, are associated with additional cancers and may have well-defined risk numbers and screening recommendations for males and females. Targeted testing for the known familial variant can clarify the cancer risks for other relatives, allowing for the initiation of appropriate increased cancer screening and risk-reducing therapies, and consideration of reproductive planning options.[27] Ultimately, it is the patient's decision and responsibility to inform at-risk relatives about their genetic test results, which underlies the importance of reviewing cascade testing and providing resources to help facilitate this transfer of critical information.

Additional Considerations

Pathogenic mutations identified in DNA-damage repair genes, such as *BRCA1/2* or mismatch repair genes, have implications for management and treatment.[3,4] Germline mutations are identified in approximately 12% of patients with metastatic PCa, but because some are not actionable, it is important to manage expectations concerning outcomes for germline testing.[7-11] Many of the genes included on PCa panels are newly associated with PCa and do not yet have well-defined cancer risks. This increases the possibility of a positive result in a gene associated with low-to-moderate increased cancer risk, which may not have clear screening recommendations. Providers need to be clear about the preliminary nature of findings and that there may not be an immediate impact on cancer screening or treatment options. Patients and their families should be encouraged to participate in registries or research studies to better characterize the risk associated with specific variants over time. Providers can refer patients to a GC for further discussion. Finally, as germline mutations continue to be levied for treatment purposes, providers must be aware of the risk of secondary malignancies and treatment-related adverse effects in some mutation carriers.[28-32]

Some providers may be concerned about the potential for negative consequences from genetic testing. A number of studies have found that most individuals are unlikely to experience significant psychological distress after receiving genetic test results.[33,34] Notably, the likelihood of psychological distress, family disruption, and nonadherence to surveillance guidelines was greater in settings without adequate patient education, counseling, informed consent, and follow-up.[33,35] A recent study of men with PCa undergoing genetic testing found genetic counseling to be beneficial.[35]

Some patients are hesitant about genetic testing because of concerns about discrimination. The Genetic Information Nondiscrimination Act (GINA), a federal law passed in 2008, protects individuals from genetic discrimination from health insurance companies and employers, with specific limitations on the type of employer and size of the company. Importantly, GINA protections do not extend to life, disability, or long-term care insurance. Some states have passed genetic discrimination laws that extend protection beyond GINA. Information regarding GINA is often included in the consent forms for testing laboratories, and summary handouts could be given to patients with additional questions.

Practical Strategies to Overcome Genetic Service Barriers

ASCO and other major health societies strongly encourage and often provide additional education training for non-genetics providers who are interested in responsibly incorporating genetic services into their practice. Courses on genomic cancer risk assessment for physicians, advanced practice providers, nurses, GCs, and other health care professionals are available through organizations such as City of Hope, American Urological Association, and ASCO.

Alternatives to in-person pretest counseling, such as educational handouts, videos, and presentations, are allowing genetic counseling expertise to be shifted to the post-test setting, prioritizing visits for complex counseling patients and/or abnormal results, and facilitating a hybrid service delivery model.[18,36] Data are still emerging regarding the

effectiveness of these models and patient satisfaction. Other practical strategies have focused on increasing GC efficiency and patient volumes, leading to the creation of new support roles, such as GC assistants; incorporation of technologies that reduce appointment time, such as online pedigree collection tools; and group genetic counseling sessions.[37,38] There are now chatbots, such as Genetic Information Assistance, that can converse with patients about family history and the basics of genetic testing and insurance, and determine who qualifies for genetic testing.

Special attention and strategies to minimize disparities in genetics are essential. It has been well documented that socioeconomically disadvantaged individuals, racial/ethnic minorities, and men are less likely to receive genetic services.[18,39-43] PCa genetic testing provides a unique opportunity for providers and institutions to address possible disparities and consider offering counseling services within a male-friendly environment. It is imperative that health care providers from all specialties work together to provide equal access to genetic services by minimizing biases, improving patient education and understanding, creating culturally sensitive interfacing materials, and expanding services to underprivileged areas.

In conclusion, as genetic testing becomes integral to the care of patients with PCa, coordinated efforts across multiple disciplines are required to deliver optimal care. Developing creative, scalable strategies to deliver high-quality personalized genetics care for patients with PCa will be paramount to realizing the full scope and impact of genetic testing for individual patients and family members. It is clear that expanding education around the need for testing and developing standardized systems for implementation in the clinic are important directions for genetics care delivery and essential for delivering precision oncology to men with PCa.

AFFILIATIONS

[1]Department of Urology, Feinberg School of Medicine at Northwestern University, Chicago, IL
[2]Seattle Cancer Care Alliance, Seattle, WA
[3]Thomas Jefferson University, Philadelphia, PA
[4]Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD
[5]Knight Cancer Institute, Oregon Health & Science University, Portland, OR
[6]Sidney Kimmel Center for Prostate and Urologic Cancers, Memorial Sloan Kettering Cancer Center, New York, NY
[7]Division of Hematology/Oncology, University of California San Francisco, CA
[8]Division of Medical Oncology, Department of Medicine, and Duke Cancer Institute, Duke University Medical Center, Durham, NC
[9]Division of Hematology and Medical Oncology, VA Portland Health Care System/Oregon Health & Science University Knight Cancer Institute, Portland, OR
[10]Division of Hematology, Oncology, and Transplantation, University of Minnesota Masonic Cancer Center, Minneapolis, MN
[11]Karmanos Cancer Institute and Department of Oncology, Wayne State University, Detroit, MI
[12]Fred Hutchinson Cancer Research Center and Division of Medical Oncology, Department of Medicine, University of Washington School of Medicine, Seattle, WA
[13]University of Wisconsin, Madison, WI
[14]Division of Hematology and Medical Oncology, Department of Medicine, Weill Cornell Medical College, New York, NY
[15]Department of Medicine, University of Chicago Comprehensive Cancer Center, Chicago, IL
[16]Department of Urology, Yale Cancer Center, New Haven, CT
[17]Department of Internal Medicine, Division of Hematology/Oncology, University of Michigan, Ann Arbor, MI; University of Michigan Rogel Cancer Center, Ann Arbor, MI
[18]Division of Hematology-Oncology, Department of Medicine, David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA
[19]Department of Medical Oncology, Dana Farber Cancer Institute, Boston, MA
[20]The Prostate Cancer Clinical Trials Consortium, New York, NY
[21]Department of Medicine, Hematology/Oncology, University of North Carolina Lineberger Cancer Center, Chapel Hill, NC
[22]Division of Hematology/Oncology, Department of Medicine, Feinberg School of Medicine at Northwestern University, Chicago, IL
[23]Department of Medicine, University of California at San Diego Moores Cancer Center, La Jolla, CA

CORRESPONDING AUTHOR

Rana R. McKay, MD, Moores Cancer Center, University of California San Diego, 3855 Health Sciences Dr, La Jolla, CA 92037; e-mail: rmckay@ucsd.edu.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/OP.20.00431.

AUTHOR CONTRIBUTIONS

Conception and design: Brittany M. Szymaniak, Lauren A. Facchini, Veda N. Giri, Emmanuel S. Antonarakis, Tomasz M. Beer, Daniel C. Danila, Daniel George, Julie N. Graff, Shilpa Gupta, Celestia S. Higano, Channing J. Paller, Charles J. Ryan, Mary-Ellen Taplin, Alicia K. Morgans, Heather H. Cheng, Rana R. McKay

Collection and assembly of data: Brittany M. Szymaniak, Lauren A. Facchini, Emmanuel S. Antonarakis, Tomasz M. Beer, Daniel C. Danila, Shilpa Gupta, Elisabeth Heath, Celestia S. Higano, Ana M. Molina, Akash Patnaik, Heather H. Cheng, Rana R. McKay

Data analysis and interpretation: Brittany M. Szymaniak, Lauren A. Facchini, Veda N. Giri, Tomasz M. Beer, Maria I. Carlo, Daniel C. Danila, Mallika Dhawan, Daniel George, Shilpa Gupta, Elisabeth Heath, Glenn Liu, Ana M. Molina, Akash Patnaik, Daniel P. Petrylak, Zachery Reichert, Matthew B. Rettig, Mary-Ellen Taplin, Jake Vinson, Young E. Whang, Heather H. Cheng, Rana R. McKay

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

B.M.S. and L.A.F. are co-first authors. A.K.M., H.H.C., and A.R.M. contributed equally to this work.

REFERENCES

1. Seyhan AA, Carini C: Are innovation and new technologies in precision medicine paving a new era in patients centric care? J Transl Med 17:114, 2019
2. Roos A, Byron SA: Genomics-enabled precision medicine for cancer. Cancer Treat Res 178:137-169, 2019
3. Zhang H, Klareskog L, Matussek A, et al: Translating genomic medicine to the clinic: Challenges and opportunities. Genome Med 11:9, 2019
4. Sachdev JC, Sandoval AC, Jahanzeb M: Update on precision medicine in breast cancer. Cancer Treat Res 178:45-80, 2019
5. Carlo MI, Giri VN, Paller CJ, et al: Evolving intersection between inherited cancer genetics and therapeutic clinical trials in prostate cancer: A white paper from the Germline Genetics Working Group of the Prostate Cancer Clinical Trials Consortium. JCO Precis Oncol 10.1200/PO.18.00060
6. Paller CJ, Antonarakis ES, Beer TM, et al: Germline genetic testing in advanced prostate cancer; practices and barriers: Survey results from the Germline Genetics Working Group of the Prostate Cancer Clinical Trials Consortium. Clin Genitourin Cancer 17:275-282.e1, 2019
7. Pritchard CC, Mateo J, Walsh MF, et al: Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med 375:443-453, 2016
8. Leongamornlert D, Saunders E, Dadaev T, et al: Frequent germline deleterious mutations in DNA repair genes in familial prostate cancer cases are associated with advanced disease. Br J Cancer 110:1663-1672, 2014
9. Isaacsson Velho P, Silberstein JL, Markowski MC, et al: Intraductal/ductal histology and lymphovascular invasion are associated with germline DNA-repair gene mutations in prostate cancer. Prostate 78:401-407, 2018
10. Abida W, Armenia J, Gopalan A, et al: Prospective genomic profiling of prostate cancer across disease states reveals germline and somatic alterations that may affect clinical decision making. JCO Precis Oncol 10.1200/PO.17.00029
11. Nicolosi P, Ledet E, Yang S, et al: Prevalence of germline variants in prostate cancer and implications for current genetic testing guidelines. JAMA Oncol 5: 523-528, 2019
12. Maiese DR, Keehn A, Lyon M, et al: Current conditions in medical genetics practice. Genet Med 21:1874-1877, 2019
13. US Bureau of Labor Statistics: Occupational employment statistics. www.bls.gov/oes/
14. Hoskovec JM, Bennett RL, Carey ME, et al: Projecting the supply and demand for certified genetic counselors: A workforce study. J Genet Couns 27:16-20, 2018
15. Bellcross CA, Kolor K, Goddard KA, et al: Awareness and utilization of BRCA1/2 testing among U.S. primary care physicians. Am J Prev Med 40:61-66, 2011
16. Plon SE, Cooper HP, Parks B, et al: Genetic testing and cancer risk management recommendations by physicians for at-risk relatives. Genet Med 13:148-154, 2011
17. Mahon SM: Errors in genetic testing: Common causes and strategies for prevention. Clin J Oncol Nurs 21:673-676, 2017
18. Cohen SA, Bradbury A, Henderson V, et al: Genetic counseling and testing in a community setting: Quality, access, and efficiency. Am Soc Clin Oncol Educ Book 39:e34-e44, 2019
19. Stoll K, Kubendran S, Cohen SA: The past, present and future of service delivery in genetic counseling: Keeping up in the era of precision medicine. Am J Med Genet C Semin Med Genet 178:24-37, 2018
20. Riconda D, Grubs RE, Campion MW, et al: Genetic counselor training for the next generation: Where do we go from here? Am J Med Genet C Semin Med Genet 178:38-45, 2018
21. Giri VN, Hyatt C, Gomella LG: Germline testing for men with prostate cancer: Navigating an expanding new world of genetic evaluation for precision therapy and precision management. J Clin Oncol 37:1455-1459, 2019
22. Daly MB, Pilarski R, Yurgelun MB, et al: NCCN guidelines insights: Genetic/familial high-risk assessment: Breast, ovarian, and pancreatic, version 1.2020. J Natl Compr Canc Netw 18:380-391, 2020
23. Tandy-Connor S, Guiltinan J, Krempely K, et al: False-positive results released by direct-to-consumer genetic tests highlight the importance of clinical confirmation testing for appropriate patient care. Genet Med 20:1515-1521, 2018
24. Riley BD, Culver JO, Skrzynia C, et al: Essential elements of genetic cancer risk assessment, counseling, and testing: Updated recommendations of the National Society of Genetic Counselors. J Genet Couns 21:151-161, 2012
25. Mandelker D, Donoghue M, Talukdar S, et al: Germline-focussed analysis of tumour-only sequencing: Recommendations from the ESMO Precision Medicine Working Group. Ann Oncol 30:1221-1231, 2019
26. Giri VN, Knudsen KE, Kelly WK, et al: Implementation of germline testing for prostate cancer: Philadelphia Prostate Cancer Consensus Conference 2019. J Clin Oncol 38:2798-2811, 2020
27. Cheng H, Powers J, Schaffer K, et al: Practical methods for integrating genetic testing into clinical practice for advanced prostate cancer. Am Soc Clin Oncol Educ Book 38:372-381, 2018
28. Mersch J, Brown N, Pirzadeh-Miller S, et al: Prevalence of variant reclassification following hereditary cancer genetic testing. JAMA 320:1266-1274, 2018
29. Macklin S, Durand N, Atwal P, et al: Observed frequency and challenges of variant reclassification in a hereditary cancer clinic. Genet Med 20:346-350, 2018
30. Puzanov I, Diab A, Abdallah K, et al: Managing toxicities associated with immune checkpoint inhibitors: Consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. J Immunother Cancer 5:95, 2017
31. Hryniewicki AT, Wang C, Shatsky RA, et al: Management of immune checkpoint inhibitor toxicities: A review and clinical guideline for emergency physicians. J Emerg Med 55:489-502, 2018
32. West AH, Knollman H, Dugan J, et al: Hematologic toxicity in BRCA1 and BRCA2 mutation carriers during chemotherapy: A retrospective matched cohort study. Cancer Med 8:5609-5618, 2019
33. Croyle RT, Achilles JS, Lerman C: Psychologic aspects of cancer genetic testing: A research update for clinicians. Cancer 80:569-575, 1997(3; suppl)
34. Meiser B: Psychological impact of genetic testing for cancer susceptibility: An update of the literature. Psycho-oncology 14:1060-1074, 2005
35. Greenberg S, Slager S, Neil BO, et al: What men want: Qualitative analysis of what men with prostate cancer (PCa) want to learn regarding genetic referral, counseling, and testing. Prostate 80:441-450, 2020
36. Buchanan AH, Rahm AK, Williams JL: Alternate service delivery models in cancer genetic counseling: A mini-review. Front Oncol 6:120, 2016
37. Hnatiuk MJ, Noss R, Mitchell AL, et al: The current state of genetic counseling assistants in the United States. J Genet Couns 28:962-973, 2019
38. McCuaig JM, Armel SR, Care M, et al: Next-generation service delivery: A scoping review of patient outcomes associated with alternative models of genetic counseling and genetic testing for hereditary cancer. Cancers (Basel) 10:435, 2018
39. Hann KEJ, Freeman M, Fraser L, et al: Awareness, knowledge, perceptions, and attitudes towards genetic testing for cancer risk among ethnic minority groups: A systematic review. BMC Public Health 17:503, 2017
40. Shields AE, Burke W, Levy DE: Differential use of available genetic tests among primary care physicians in the United States: Results of a national survey. Genet Med 10:404-414, 2008

41. Childers KK, Maggard-Gibbons M, Macinko J, et al: National distribution of cancer genetic testing in the United States: Evidence for a gender disparity in hereditary breast and ovarian cancer. JAMA Oncol 4:876-879, 2018
42. Pritchard CC: New name for breast-cancer syndrome could help to save lives. Nature 571:27-29, 2019
43. Rauscher EA, Dean M: "I've just never gotten around to doing it": Men's approaches to managing BRCA-related cancer risks. Patient Educ Couns 101:340-345, 2018
44. Mohler JL, Srinivas S, Antonarakis ES, et al: Prostate cancer, version 1.2020, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 17: 479-505, 2020
45. Giri VN, Knudsen KE, Kelly WK, et al: Role of genetic testing for inherited prostate cancer risk: Philadelphia Prostate Cancer Consensus Conference 2017. J Clin Oncol 36:414-424, 2018
46. Sanda MG, Cadeddu JA, Kirkby E, et al: Clinically localized prostate cancer: AUA/ASTRO/SUO guideline. Part I: Risk stratification, shared decision making, and care options. J Urol 199:683-690, 2018
47. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 17:405-424, 2015
48. Adam MP, Ardinger HH, Pagon RA (eds): GeneReviews [Internet]. https://www.ncbi.nlm.nih.gov/books/NBK5191/
49. American College of Medical Genetics: Genetic Susceptibility to Breast and Ovarian Cancer: Assessment, Counseling and Testing Guidelines. https://www.ncbi.nlm.nih.gov/books/NBK56955/

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Practical Considerations and Challenges for Germline Genetic Testing in Patients With Prostate Cancer: Recommendations From the Germline Genetics Working Group of the PCCTC

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/op/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Brittany M. Szymaniak
Honoraria: Invitae Corporation, Urogpo
Consulting or Advisory Role: Clovis Oncology
Uncompensated Relationships: Urogpo

Veda N. Giri
Stock and Other Ownership Interests: Novopyxis (I)
Speakers' Bureau: Janssen

Emmanuel S. Antonarakis
Honoraria: Sanofi, Dendreon, Medivation, Janssen Biotech, Essa, Astellas Pharma, Merck, AstraZeneca, Clovis Oncology
Consulting or Advisory Role: Sanofi, Dendreon, Janssen Biotech, Essa, Merck, AstraZeneca, Clovis Oncology, Lilly, Bayer
Research Funding: Janssen Biotech (Inst), Johnson & Johnson (Inst), Sanofi (Inst), Dendreon (Inst), Aragon Pharmaceuticals (Inst), Exelixis (Inst), Millennium (Inst), Genentech (Inst), Novartis (Inst), Astellas Pharma (Inst), Tokai Pharmaceuticals (Inst), Merck (Inst), AstraZeneca (Inst), Clovis Oncology (Inst), Constellation Pharmaceuticals (Inst)
Patents, Royalties, Other Intellectual Property: Co-inventor of a biomarker technology that has been licensed to Qiagen
Travel, Accommodations, Expenses: Sanofi, Dendreon, Medivation

Tomasz M. Beer
Stock and Other Ownership Interests: Salarius Pharmaceuticals, Arvinas
Consulting or Advisory Role: Astellas Pharma, AstraZeneca, Bayer, Bristol Myers Squibb, Clovis Oncology, GlaxoSmithKline, Novartis, Pfizer, Arvinas, Tolero Pharmaceuticals
Research Funding: Alliance Foundation Trials (Inst), Astellas (Inst), Boehringer Ingelheim (Inst), Corcept Therapeutics (Inst), Endocyte (Inst), Janssen Research & Development (Inst), Harpoon Therapeutics (Inst), Medivation (Inst), Sotio (Inst), Theraclone Sciences (Inst), Zenith Epigenetics (Inst)

Maria I. Carlo
Consulting or Advisory Role: Pfizer
Other Relationship: Prostate Cancer Foundation, Robert Wood Johnson Foundation

Daniel C. Danila
Honoraria: Angle, Bayer, ScreenCell, Janssen Oncology, Pfizer, AxImmune, Clovis Oncology, Astellas Pharma
Consulting or Advisory Role: Angle, Bayer, Sanador, AxImmune, Pfizer, Clovis Oncology, Astellas Pharma, Janssen Scientific Affairs
Research Funding: Prostate Cancer Foundation, Genentech, Janssen Research Development (Inst)
Patents, Royalties, Other Intellectual Property: Gene expression profile associated with prostate cancer
Travel, Accommodations, Expenses: Cambridge Healthtech Institute, Prostate Cancer Foundation, ScreenCell, StopCancer, American Austrian Open Medical Institute, Janssen Biotech, Genzyme, Pfizer, Janssen Scientific Affairs, Astellas Pharma

Daniel George
Leadership: Capio BioSciences
Honoraria: Sanofi, Bayer, Exelixis, EMD Serono, OncLive, Pfizer, UroToday, Acceleron Pharma, American Association for Cancer Research, Axess Oncology, Janssen Oncology, Millennium Medical Publishing
Consulting or Advisory Role: Bayer, Exelixis, Pfizer, Sanofi, Astellas Pharma, Innocrin Pharma, Bristol Myers Squibb, Genentech, Janssen, Merck Sharp & Dohme, Myovant Sciences, AstraZeneca, Michael J. Hennessy Associates, Vizuri Health Sciences
Speakers' Bureau: Sanofi, Bayer, Exelixis
Research Funding: Exelixis (Inst), Janssen Oncology (Inst), Novartis (Inst), Pfizer (Inst), Astellas Pharma (Inst), Bristol Myers Squibb (Inst), Acerta Pharma (Inst), Bayer (Inst), Dendreon (Inst), Innocrin Pharma (Inst), Calithera Biosciences (Inst), Sanofi/Aventis (Inst)
Travel, Accommodations, Expenses: Bayer, Exelixis, Merck, Pfizer, Sanofi, Janssen Oncology, UroToday

Julie N. Graff
Honoraria: Janssen Oncology, Valeant/Dendreon, Bayer, Sanofi, Astellas Medivation
Consulting or Advisory Role: Exelixis
Speakers' Bureau: i3 CME
Research Funding: Sanofi (Inst), Medivation (Inst), Merck Sharp & Dohme (Inst), Janssen Oncology (Inst)
Patents, Royalties, Other Intellectual Property: Oncoresponse: Exceptional responders
Travel, Accommodations, Expenses: Bayer, Merck Sharp & Dohme, Clovis Oncology, Sanofi

Shilpa Gupta
Stock and Other Ownership Interests: Nektar
Honoraria: Janssen Oncology, AstraZeneca, Exelixis, Bristol Myers Squibb, Merck Sharp & Dohme, Seattle Genetics, Pfizer
Speakers' Bureau: Bristol Myers Squibb, Janssen Oncology, Exelixis
Research Funding: Merck, Pfizer, Bristol Myers Squibb, Seattle Genetics

Elisabeth Heath
Honoraria: Bayer, Dendreon, Sanofi, Seattle Genetics
Consulting or Advisory Role: Agensys, Bayer, Dendreon
Speakers' Bureau: Sanofi
Research Funding: Tokai Pharmaceuticals (Inst), Seattle Genetics (Inst), Agensys (Inst), Dendreon (Inst), Genentech (Inst), Millennium (Inst), Celldex (Inst), Inovio Pharmaceuticals (Inst), Celgene (Inst), Zenith Epigenetics (Inst), Merck (Inst), AstraZeneca (Inst), Esanik (Inst), Zenith Epigenetics (Inst), Oncolys BioPharma (Inst), Curemeta (Inst), Bristol Myers Squibb (Inst), eFFECTOR Therapeutics (Inst), Fortis (Inst), Astellas Pharma (Inst), Medivation (Inst), Ignyta (Inst), Synta (Inst), Caris Life Sciences (Inst), Boehringer Ingelheim (Inst), GlaxoSmithKline (Inst), Merck Sharp & Dohme (Inst), Plexxikon (Inst), Corcept Therapeutics (Inst), Infinity Pharmaceuticals (Inst), Bayer (Inst), Modra Pharmaceuticals (Inst), Pellficure Pharmaceuticals (Inst), Champions Oncology (Inst), AIQ Solutions (Inst), Novartis Pharmaceuticals (Inst), Janssen Research & Development (Inst), Mirati Therapeutics (Inst), Peloton (Inst), Daiichi Sankyo (Inst), Calibr (Inst), Eisai (Inst), Pharmacyclics (Inst), FivePrime Therapeutics (Inst)
Travel, Accommodations, Expenses: Agensys, Bayer, Sanofi
Other Relationship: Caris Centers of Excellence

Celestia S. Higano
Honoraria: Astellas Pharma
Consulting or Advisory Role: Bayer, Ferring, Clovis Oncology, Blue Earth Diagnostics, Janssen, Hinova, Pfizer, AstraZeneca, Carrick Therapeutics, Novartis, Merck Sharp & Dohme
Research Funding: Aragon Pharmaceuticals (Inst), AstraZeneca (Inst), Medivation (Inst), Emergent BioSolutions (Inst), Bayer (Inst), Pfizer (Inst), Roche (Inst), Astellas Pharma (Inst), Clovis Oncology (Inst), Ferring Pharmaceuticals (Inst), eFFECTOR Therapeutics (Inst)
Travel, Accommodations, Expenses: Bayer, Clovis Oncology, Blue Earth Diagnostics, Ferring, Pfizer, Hinova Pharmaceuticals, Janssen Oncology, Novartis, Merck Sharp & Dohme, Carrick Therapeutics

Glenn Liu
Employment: AIQ Solutions
Leadership: AIQ Solutions
Stock and Other Ownership Interests: AIQ Solutions
Consulting or Advisory Role: Novartis, Exelixis, Tricon Pharmaceuticals
Research Funding: Johnson & Johnson (Inst), Novartis (Inst), Madison Vaccines, Pfizer, Tracon Pharma
Patents, Royalties, Other Intellectual Property: I have a patent pending titled "System and method for evaluation of disease burden," which provides a novel method to identify and quantitate treatment response (Inst)
Travel, Accommodations, Expenses: AIQ Solutions, Tracon Pharma

Ana M. Molina
Honoraria: ASCO
Consulting or Advisory Role: Eisai, Exelixis, Novartis, Janssen

Channing J. Paller
Consulting or Advisory Role: Dendreon, Omnitura
Research Funding: Lilly (Inst)

Akash Patnaik
Stock and Other Ownership Interests: Gilead, Genentech, Merck, Prime Oncology, Jounce Therapeutics, Exelixis
Consulting or Advisory Role: Jounce Therapeutics, Exelixis, Guidepoint, Gerhson Lehrman Group
Research Funding: Bristol Myers Squibb (Inst), Progenics (Inst), Clovis Oncology (Inst)
Travel, Accommodations, Expenses: Bristol Myers Squibb, Prime Oncology, Exelixis

Daniel P. Petrylak
Stock and Other Ownership Interests: Bellicum Pharmaceuticals, TYME
Consulting or Advisory Role: Bayer, Exelixis, Pfizer, Roche, Astellas Pharma, AstraZeneca, Lilly, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Clovis Oncology, Incyte, Janssen, Pharmacyclics, Seattle Genetics, Urogen Pharma, Advanced Accelerator Applications, Ipsen
Research Funding: Progenics (Inst), Sanofi (Inst), Endocyte (Inst), Genentech (Inst), Merck (Inst), Astellas Medivation (Inst), Novartis (Inst), AstraZeneca (Inst), Bayer (Inst), Lilly (Inst), Innocrin Pharma (Inst), MedImmune (Inst), Pfizer (Inst), Roche (Inst), Seattle Genetics (Inst), Clovis Oncology (Inst), Bristol Myers Squibb (Inst), Advanced Accelerator Applications (Inst)
Expert Testimony: Celgene, Sanofi

Zachery Reichert
Consulting or Advisory Role: Dendreon
Research Funding: AstraZeneca (Inst)

Matthew Rettig
Consulting or Advisory Role: Johnson & Johnson, Ambrx, Amgen, Clovis
Speakers' Bureau: Johnson & Johnson, Bayer
Research Funding: Novartis (Inst), Astellas Medivation (Inst), Johnson & Johnson (Inst)
Patents, Royalties, Other Intellectual Property: I am a co-inventor on a patent for novel inhibitors of the N-terminal domain of the AR. There are no commercial partnerships as of yet.
Travel, Accommodations, Expenses: Johnson & Johnson

Charles J. Ryan
Honoraria: Janssen Oncology, Bayer
Consulting or Advisory Role: Bayer, Dendreon, AAA, Myovant Sciences, Clovis Oncology (Inst), Roivant, Clovis Oncology (Inst), Sanofi Genzyme (Inst)

Mary-Ellen Taplin
Honoraria: Janssen-Ortho, Clovis Oncology, Astellas Pharma, Incyte, UpToDate, Research to Practice, Pfizer, Bayer, Amgen, AstraZeneca, Progenics, Guidepoint Global, Celegen, Merck, GSK, Myovant, Roivant Sciences
Consulting or Advisory Role: Janssen-Ortho, Bayer, Guidepoint Global, Best Doctors, UpToDate, Clovis Oncology, Research to Practice, Myovant Sciences, Incyte, Pfizer, AstraZeneca, Arcus (I)
Research Funding: Janssen-Ortho (Inst), Medivation (Inst), Bayer (Inst), Pfizer (Inst)
Travel, Accommodations, Expenses: Medivation, Janssen Oncology, Tokai Pharmaceuticals, Astellas Pharma, Incyte, Pfizer, Clovis Oncology, Bayer

Young E. Whang
Research Funding: Astellas Pharma (Inst), Clovis Oncology (Inst), Constellation Pharmaceuticals (Inst), Amgen (Inst)

Alicia K. Morgans
Honoraria: Genentech, Janssen, Sanofi, AstraZeneca, Astellas Scientific and Medical Affairs, Astellas Colombia, Janssen Oncology, Bayer
Consulting or Advisory Role: Genentech, AstraZeneca, Sanofi, Bayer, Astellas Pharma, Janssen, Advanced Accelerator Applications, Myovant Sciences
Research Funding: Bayer, Seattle Genetics/Astellas, Genentech, AstraZeneca, Astellas Scientific and Medical Affairs
Travel, Accommodations, Expenses: Sanofi

Heather H. Cheng
Consulting or Advisory Role: AstraZeneca (Inst)
Research Funding: Sanofi (Inst), Janssen (Inst), Clovis Oncology (Inst), Color Foundation (Inst), Fred Hutchinson Cancer Research Center (Inst)

Rana R. McKay
Consulting or Advisory Role: Janssen, Novartis, Tempus, Exelixis, Pfizer, Bristol Myers Squibb, Astellas Medivation, Dendreon, Vividion, Bayer, Sanofi
Research Funding: Pfizer (Inst), Bayer (Inst)

Heather H. Cheng
Research Funding: Inovio Pharmaceuticals, Sanofi, Astellas Medivation, Janssen, Clovis Oncology, Color Foundation (Inst)

No other potential conflicts of interest were reported.

JAMA Oncology
View Article

JAMA Oncol. 2021 Jan; 7(1): 107–110.
Published online 2020 Nov 5.
doi: 10.1001/jamaoncol.2020.5161: 10.1001/jamaoncol.2020.5161

PMCID: PMC7645740
PMID: 33151258

Association of Clonal Hematopoiesis in DNA Repair Genes With Prostate Cancer Plasma Cell-free DNA Testing Interference

Kendal Jensen, MD, PhD,[1] Eric Q. Konnick, MD,[1] Michael T. Schweizer, MD,[2,3,4] Alexandra O. Sokolova, MD,[2] Petros Grivas, MD, PhD,[2,4] Heather H. Cheng, MD, PhD,[2,3,4] Nola M. Klemfuss, MHA,[4] Mallory Beightol, BS, MB,[1] Evan Y. Yu, MD,[2,3] Peter S. Nelson, MD,[2,3,5] Bruce Montgomery, MD,[2,4] and Colin C. Pritchard, MD, PhD[1,3]

[1]Department of Laboratory Medicine, University of Washington, Seattle
[2]Department of Medicine, Division of Medical Oncology, University of Washington, Seattle
[3]Brotman Baty Institute for Precision Medicine, Seattle, Washington
[4]Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington
[5]Human Biology Division, Fred Hutchinson Cancer Research Center, Seattle, Washington
Corresponding author.

Article Information

Accepted for Publication: August 13, 2020.

Published Online: November 5, 2020. doi:10.1001/jamaoncol.2020.5161

Corresponding Author: Colin C. Pritchard, MD, PhD, University of Washington, 1959 NE Pacific St, PO Box 357110, Seattle, WA 98195 (cpritch@uw.edu).

Author Contributions: Dr Pritchard had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Jensen, Sokolova, Nelson, Pritchard.

Acquisition, analysis, or interpretation of data: Jensen, Konnick, Schweizer, Grivas, Cheng, Klemfuss, Beightol, Yu, Montgomery, Pritchard.

Drafting of the manuscript: Jensen, Konnick, Schweizer, Beightol, Nelson, Pritchard.

Critical revision of the manuscript for important intellectual content: Jensen, Konnick, Schweizer, Sokolova, Grivas, Cheng, Klemfuss, Yu, Montgomery, Pritchard.

Statistical analysis: Jensen, Pritchard.

Obtained funding: Nelson, Pritchard.

Administrative, technical, or material support: Konnick, Cheng, Klemfuss, Beightol, Yu, Nelson, Montgomery, Pritchard.

Supervision: Konnick, Pritchard.

Conflict of Interest Disclosures: Dr Pritchard consults for AstraZeneca and Promega. Dr Grivas consults for AstraZeneca, Bayer, Bristol Myers Squibb, Clovis Oncology, Driver, EMD Serono, Exelixis, Foundation Medicine, GlaxoSmithKline, Genentech, Genzyme, Heron Therapeutics, Janssen, Merck, Mirati Therapeutics, Pfizer, Roche, Seattle Genetics, and QED Therapeutics; he also reports participation in an educational program for Bristol Myers Squibb; and institutional research funding from AstraZeneca, Bavarian Nordic, Bayer, Bristol Myers Squibb, Clovis Oncology, Debiopharm, Genentech, Immunomedics, Kure It Cancer Research, Merck, Mirati Therapeutics, Oncogenex, Pfizer, and QED Therapeutics. No other conflicts were reported.

Funding/Support: This work was supported by US Department of Defense awards W81XWH-18-1-0756 (PC170510) (design and conduct of the study), W81XWH-18-1-0356 (PC170503P2) (design and conduct of the study), W81XWH-18-1-0354 (design and conduct of the study), and W81XWH-16-1-0484 (design and conduct of the study), the Pacific Northwest Prostate Cancer SPORE CA097186, the Brotman Baty Institute for Precision Medicine (design and conduct of the study), the Prostate Cancer Foundation (design and conduct of the study), the UW/FHCRC Institute for Prostate Cancer Research (IPCR) (design and conduct of the study, collection, management, analysis, and interpretation of the data), and National Institutes of Health/National Cancer Institute Cancer Center Support Grant P30 CA015704 (design and conduct of the study).

Role of the Funder/Sponsor: The funding agencies had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Received 2020 Jun 17; Accepted 2020 Aug 13.

Key Points

Question

How often are cell-free DNA (cfDNA) studies in prostate cancer confounded by clonal hematopoiesis (CHIP) variants in genes used for poly(ADP) ribose polymerase inhibitor (PARPi) eligibility?

Findings

In this case series study of 69 men with advanced prostate cancer, 7 (10%) had CHIP variants in genes used for US Food and Drug Administration-approved indications of PARPi treatment, most frequently in *ATM*.

Meaning

Men with prostate cancer are at high risk of being misdiagnosed as being eligible for PARPi therapy using current cfDNA tests; assays should use a whole-blood control sample to distinguish CHIP variants from prostate cancer.

Abstract

Importance

Cell-free DNA (cfDNA) testing is increasingly used in the treatment of patients with advanced prostate cancer. Clonal hematopoiesis of indeterminate potential (CHIP) can interfere with cfDNA testing and cause incorrect interpretation of results. There is an urgent need to better understand this problem

following recent US Food and Drug Administration approval of poly(ADP) ribose polymerase inhibitors (PARPi) for metastatic prostate cancer based on variants in DNA repair genes that can be affected by CHIP.

Objective

To determine the prevalence of clinically relevant CHIP interference in prostate cancer cfDNA testing.

Design, Setting, and Participants

We report a case series of 69 patients with advanced prostate cancer (metastatic disease or with rising PSA following localized therapy) who had cfDNA variant testing with a large panel cancer next generation sequencing assay (UW-OncoPlexCT). To determine the source of variants in plasma, we tested paired cfDNA and whole blood control samples. The study was carried out in an academic medical center system reference laboratory.

Main Outcomes and Measures

Prevalence and gene spectrum of CHIP interference in patients with prostate cancer undergoing cfDNA testing.

Results

We detected CHIP variants at 2% or more variant fraction in cfDNA from 13 of 69 men with prostate cancer (19%; 95% CI, 10%-30%). Seven men (10%; 95% CI, 4%-20%) had CHIP variants in DNA repair genes used to determine PARPi candidacy, including *ATM* (n = 5), *BRCA2* (n = 1), and *CHEK2* (n = 1). Overall, CHIP variants accounted for almost half of the somatic DNA repair gene variants detected. Participant CHIP variants were exponentially correlated with older age ($R^2 = 0.82$). CHIP interference variants could be distinguished from prostate cancer variants using a paired whole-blood control.

Conclusions and Relevance

In this case series, approximately 10% of men with advanced prostate cancer had CHIP interference in plasma cfDNA in DNA repair genes that are used for eligibility of PARPi therapy, most frequently in *ATM*. Clinical cfDNA testing should include a paired whole-blood control to exclude CHIP variants and avoid misdiagnosis.

Introduction

Cell-free DNA (cfDNA) variant analysis is used to guide treatment decisions for men with metastatic prostate cancer (mPC) and to enroll patients on clinical trials.[1] Two poly(ADP) ribose polymerase inhibitors (PARPi) were recently granted US Food and Drug Administration (FDA) approval for use in selected patients with mPC based on DNA repair gene status: rucaparib for patients with *BRCA1* or *BRCA2* variants and olaparib for patients with *ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D* or *RAD51L* variants.[2] Following these biomarker-guided approvals we expect cfDNA testing will sharply increase for patients with mPC because it offers the convenience and simplicity of testing on a blood sample in the advanced disease setting.[1,3,4] Thus, there is an urgent need to understand cfDNA testing performance and sources of test interferences.

Clonal hematopoiesis of indeterminate potential (CHIP) is a known confounder of cfDNA testing.[5,6] Clonal hematopoiesis of indeterminate potential variants are detected in both plasma and whole blood, whereas prostate cancer variants are detected in plasma only. Yet most commercial labs perform cfDNA testing using a plasma-only approach that cannot reliably distinguish variants derived from prostate cancer

vs those arising from CHIP. To improve cfDNA assay performance, we developed an approach (UW-OncoPlexCT) that simultaneously analyzes plasma and paired whole-blood control samples.[4] Using this paired testing approach we sought to determine to what degree CHIP interferes with the results of prostate cancer cfDNA testing.

Methods

We retrospectively reviewed cfDNA study results from 69 patients with advanced prostate cancer (metastatic disease or with rising PSA following localized therapy) sequenced by our Clinical Laboratory Improvement Amendments (CLIA)-certified and College of American Pathologists (CAP)-accredited clinical UW-OncoPlexCT protocol. Plasma cfDNA and a paired whole-blood control sample were tested in every patient.[4,7] We defined CHIP interference as a pathogenic variant with variant allele fractions (VAFs) of at least 2% in both the whole blood and plasma. Germline variants were distinguished from CHIP clones by tumor sequencing. Sequencing data analysis and variant interpretation were performed by an expert molecular pathologist (C.C.P.). All data were manually reviewed in the integrated genomics viewer (IGV) to exclude sequencing artifacts. Data were generated and preprocessed by the University of Washington NGS Laboratory and Analytics group. This study was performed in accordance with the Declaration of Helsinki guidelines and approved by the University of Washington/Fred Hutchinson Cancer Consortium institutional review board and all patients provided written informed consent.

Results

We detected CHIP interference clones at least 2% variant fraction in 13 of 69 patients (19%; 95% CI, 10%-30%). Seven patients (10%; 95% CI, 4%-20%) had CHIP variants in DNA repair genes that are used for PARPi selection (*ATM* n = 5, *BRCA2*, n = 1 and *CHEK2*, n = *1*) (Figure) (Table). The 6 remaining patients had CHIP interference in genes frequently impacted by CHIP: *ASXL1*, *DNMT3A*, *PTEN*, *TET2*, and *TP53* (Figure) (eFigure in the Supplement).[8,9]

We observed that CHIP interference correlated exponentially with increasing age ($R^2 = 0.82$). We detected CHIP in 0% (0/6) of men aged 40 to 50 years, 12.5% (2/16) of men aged 51 to 60 years, 6.3% (1/16) of men aged 61 to 70 years, 20.8% (5/24) of men aged 71 to 80 years, and 71% (5/7) of men aged 81 to 90 years (Figure, A).

In 20 patients with advanced prostate cancer, we detected a total of 23 pathogenic variants in DNA repair gene variants used for selection of PARPi therapy, from the following source(s): CHIP interference somatic (n = 8, 1 patient had 2), non-CHIP somatic (n = 9), germline (n = 6) (Figure, B). We considered germline variants and non-CHIP somatic variants as true positives (n = 15) and CHIP interference as false positives (n = 8). Restricting the assay to a plasma-only analysis, only 65% of DNA repair gene variants detected were true positives (15/23). When incorporating a paired whole-blood control to remove CHIP interference, all DNA repair gene variants were true positives (15/15, 100%).

The patient with *BRCA2* CHIP interference had cfDNA testing done in parallel by an outside commercial laboratory using a plasma-only assay, which was unknown to our laboratory at the time of testing. The *BRCA2* CHIP clone was clinically reported by the commercial lab with the recommendation to use PARPi therapy.

Discussion

We found that a strikingly high proportion of DNA repair gene variants in the plasma of patients with advanced prostate cancer are attributable to CHIP. The CHIP variants were strongly correlated with increased age, and even higher than expected by age group. The high rate of CHIP may also be influenced by prior exposure to chemotherapy.[10,11] We are concerned that CHIP interference is causing false-positive cfDNA biomarker assessments that may result in patient harm from inappropriate treatment, and delays in

delivering alternative effective treatment options. Without performing a whole-blood control, 7 of 69 patients (10%) would have been misdiagnosed and incorrectly deemed eligible for PARP-inhibitor therapy based on CHIP interference in plasma. In fact, 1 patient in this series had a *BRCA2* CHIP clone that had been previously reported by a commercial lab with the recommendation to use a PARPi. To mitigate these risks, cfDNA results should be compared to results from whole-blood control or tumor tissue.[12]

Challenges of accurate cfDNA testing are beginning to be described. A recent report[13] highlighted inaccuracies of commercial laboratory cfDNA testing in patients with prostate cancer. In that report, cfDNA samples from 40 patients were sent to 2 separate CLIA-certified laboratories and only 9 of 40 (23%) demonstrated congruence (complete or partial) of positive findings.[13] The consistent findings included *ATM* and *TP53* variants in patients with low PSA at the time of blood draw, raising suspicion that these may be CHIP clones. The CHIP interference in cfDNA testing has also been reported in other cancer types. In renal-cell carcinoma (RCC), for example, CHIP was found to affect cfDNA results in 43% of patients.[14]

Overall, *ATM* accounted for the majority of clinically relevant CHIP interference in our series. The *ATM* gene has been described as a frequent CHIP clone in clinical cancer predisposition testing, along with *CHEK2* and *TP53*.[10] We speculate that CHIP interference in cfDNA testing could be affecting results of PARPi clinical studies of patients with metastatic prostate cancer. Trials allowing plasma-only cfDNA testing for enrollment may have included patients with false-positive results associated with CHIP in DNA repair genes, particularly in *ATM*.[15] We speculate that this could be contributing to low PARPi response rates reported in patients with *ATM* variants, such as recently reported from the TRITON2 study.[15]

Limitations

This study has several limitations including relatively small sample size, the retrospective nature of the study, and heterogeneity in patient populations and prior therapies.

Conclusions

Findings of this study suggest that CHIP substantially interferes with plasma cfDNA testing in patients with advanced prostate cancer. There is a risk for widespread misdiagnosis and overtreatment of men with PARPi using currently available commercial cfDNA assays. We recommend that all cfDNA testing in patients with prostate cancer include a whole-blood control to distinguish CHIP from prostate cancer variants.

Notes

Supplement.

eFigure. All Variants Detected in Plasma Cell-Free DNA From 69 Men With Advanced Prostate Cancer. Each column represents 1 unique patient sorted by age.

References

1. Goodall J, Mateo J, Yuan W, et al. ; TOPARP-A investigators . Circulating cell-free DNA to guide prostate cancer treatment with PARP inhibition. *Cancer Discov*. 2017;7(9):1006-1017. doi:10.1158/2159-8290.CD-17-0261 [PMCID: PMC6143169] [PubMed: 28450425] [CrossRef: 10.1158/2159-8290.CD-17-0261]

2. de Bono J, Mateo J, Fizazi K, et al. . Olaparib for metastatic castration-resistant prostate cancer. *N Engl J Med*. 2020;382(22):2091-2102. doi:10.1056/NEJMoa1911440 [PubMed: 32343890] [CrossRef: 10.1056/NEJMoa1911440]

3. Annala M, Vandekerkhove G, Khalaf D, et al. . Circulating tumor DNA genomics correlate with resistance to abiraterone and enzalutamide in prostate cancer. *Cancer Discov*. 2018;8(4):444-457. doi:10.1158/2159-8290.CD-17-0937 [PubMed: 29367197] [CrossRef: 10.1158/2159-8290.CD-17-0937]

4. Schweizer MT, Gulati R, Beightol M, et al. . Clinical determinants for successful circulating tumor DNA analysis in prostate cancer. *Prostate*. 2019;79(7):701-708. doi:10.1002/pros.23778 [PMCID: PMC6589085] [PubMed: 30865311] [CrossRef: 10.1002/pros.23778]

5. Weitzel JN, Chao EC, Nehoray B, et al. . Somatic TP53 variants frequently confound germ-line testing results. *Genet Med*. 2018;20(8):809-816. doi:10.1038/gim.2017.196 [PMCID: PMC5976505] [PubMed: 29189820] [CrossRef: 10.1038/gim.2017.196]

6. Razavi P, Li BT, Brown DN, et al. . High-intensity sequencing reveals the sources of plasma circulating cell-free DNA variants. *Nat Med*. 2019;25(12):1928-1937. doi:10.1038/s41591-019-0652-7 [PMCID: PMC7061455] [PubMed: 31768066] [CrossRef: 10.1038/s41591-019-0652-7]

7. Kuo AJ, Paulson VA, Hempelmann JA, et al. . Validation and implementation of a modular targeted capture assay for the detection of clinically significant molecular oncology alterations. *Pract Lab Med*. 2020;19:e00153. doi:10.1016/j.plabm.2020.e00153 [PMCID: PMC7038441] [PubMed: 32123717] [CrossRef: 10.1016/j.plabm.2020.e00153]

8. Genovese G, Kähler AK, Handsaker RE, et al. . Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. *N Engl J Med*. 2014;371(26):2477-2487. doi:10.1056/NEJMoa1409405 [PMCID: PMC4290021] [PubMed: 25426838] [CrossRef: 10.1056/NEJMoa1409405]

9. Jaiswal S, Fontanillas P, Flannick J, et al. . Age-related clonal hematopoiesis associated with adverse outcomes. *N Engl J Med*. 2014;371(26):2488-2498. doi:10.1056/NEJMoa1408617 [PMCID: PMC4306669] [PubMed: 25426837] [CrossRef: 10.1056/NEJMoa1408617]

10. Slavin TP, Coffee B, Bernhisel R, et al. . Prevalence and characteristics of likely-somatic variants in cancer susceptibility genes among individuals who had hereditary pan-cancer panel testing. *Cancer Genet*. 2019;235-236:31-38. doi:10.1016/j.cancergen.2019.04.005 [PMCID: PMC6625900] [PubMed: 31056428] [CrossRef: 10.1016/j.cancergen.2019.04.005]

11. Swisher EM, Harrell MI, Norquist BM, et al. . Somatic mosaic mutations in PPM1D and TP53 in the blood of women with ovarian carcinoma. *JAMA Oncol*. 2016;2(3):370-372. doi:10.1001/jamaoncol.2015.6053 [PMCID: PMC4865293] [PubMed: 26847329] [CrossRef: 10.1001/jamaoncol.2015.6053]

12. Mateo J, Carreira S, Sandhu S, et al. . DNA-repair defects and olaparib in metastatic prostate cancer. *N Engl J Med*. 2015;373(18):1697-1708. doi:10.1056/NEJMoa1506859 [PMCID: PMC5228595] [PubMed: 26510020] [CrossRef: 10.1056/NEJMoa1506859]

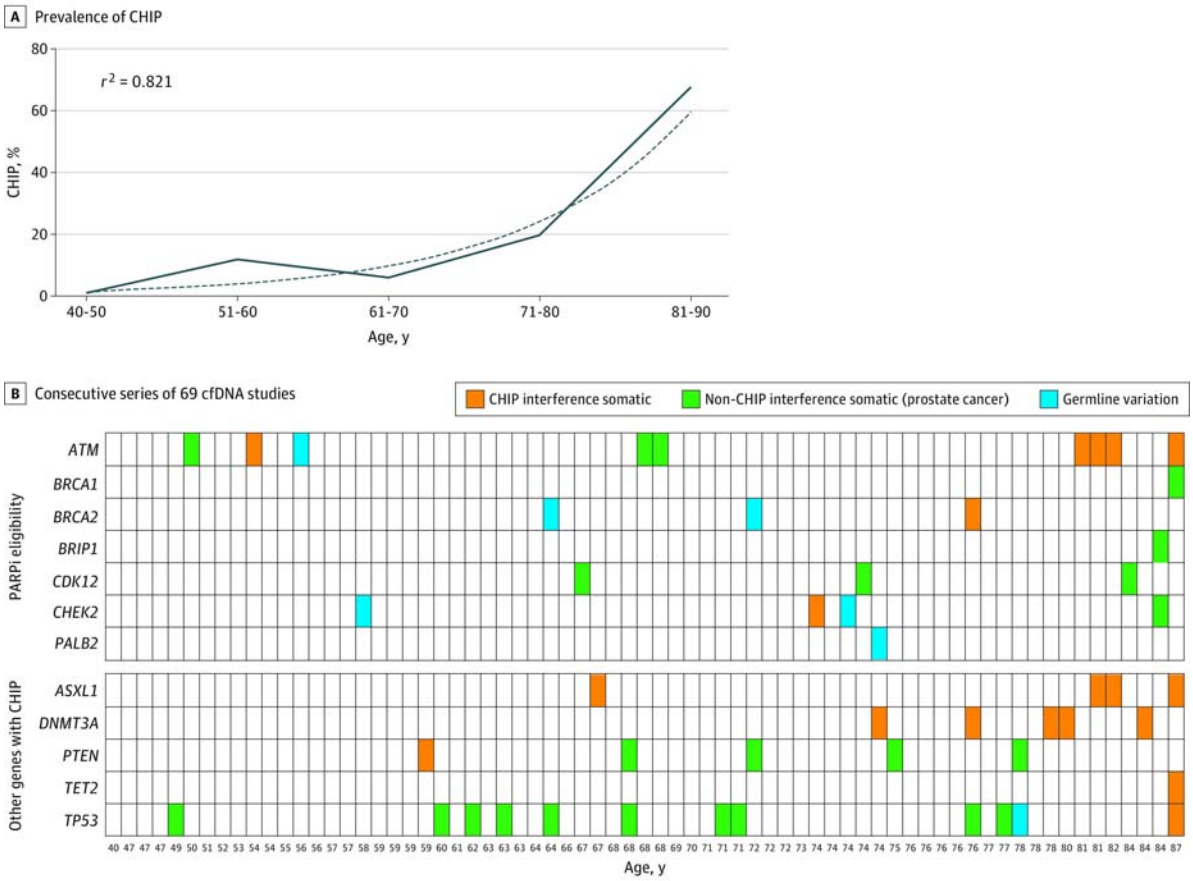
13. Torga G, Pienta KJ. Patient-paired sample congruence between 2 commercial liquid biopsy tests. *JAMA Oncol*. 2018;4(6):868-870. doi:10.1001/jamaoncol.2017.4027 [PMCID: PMC6145681] [PubMed: 29242909] [CrossRef: 10.1001/jamaoncol.2017.4027]

14. Bacon JVW, Annala M, Soleimani M, et al. . Plasma circulating tumor DNA and clonal hematopoiesis in metastatic renal cell carcinoma. *Clin Genitourin Cancer*. 2020;18(4):322-331.e2. doi:10.1016/j.clgc.2019.12.018 [PubMed: 32046920] [CrossRef: 10.1016/j.clgc.2019.12.018]

15. Abida W, Campbell D, Patnaik A, et al. . Non-BRCA DNA damage repair gene alterations and response to the PARP inhibitor rucaparib in metastatic castration-resistant prostate cancer: analysis from the phase II TRITON2 study. *Clin Cancer Res*. 2020;26(11):2487-2496. doi:10.1158/1078-0432.CCR-20-0394 [PubMed: 32086346] [CrossRef: 10.1158/1078-0432.CCR-20-0394]

Figures and Tables

Figure.



Source of Variants Detected in Prostate Cancer cfDNA Studies

A, The prevalence of CHIP variants increased with age. CHIP was particularly prevalent (71%) in the 81 to 90 year age range. B, Consecutive series of 69 cfDNA studies. The DNA repair genes associated with PARPi eligibility are depicted along with other genes in which CHIP was detected. Each column represents 1 unique patient sorted by age. Variants detected in plasma are color coded by source, red indicates CHIP interference, somatic; green indicates non-CHIP, somatic (prostate cancer); yellow indicates germline. cfDNA indicates cell-free DNA; CHIP, clonal hematopoiesis of indeterminate potential; PARPi, poly(ADP) ribose polymerase inhibitor.

Table.

CHIP Clones Detected in DNA Repair Genes Used for PARPi Eligibility

Age, y	Gene[a]	CHIP Variant(s)	VAF cfDNA	VAF blood control	Notes
81	*ATM*	p.R3008C, p.E3007D	16%; 5%	16%; 5%	CHIP hotspot, reported by outside lab in bone marrow
54	ATM	p.S305*	2%	3%	
82	*ATM*	p.G2891D	12%	13%	Kinase domain
81	*ATM*	c.2921 + 1G>A	78%	65%	Not germline based on tumor testing
87	*ATM*	p.L2492R	7%	9%	CHIP hotspot
76	*BRCA2*	p.T3310Nfs*17	3%	3%	Reported by outside lab, recommending PARPi
74	*CHEK2*	p.P426H	19%	18%	Kinase domain

Abbreviations: CHIP, clonal hematopoiesis of indeterminate potential; VAF, variant allele fraction; PARPi, poly(ADP) ribose polymerase inhibitor.

[a]*ATM* reference sequence: NM_000051.3, *BRCA2* reference sequence NM_000059.3; *CHEK2* reference sequence: NM_007194.3.

HHS Public Access

Author manuscript

Clin Cancer Res. Author manuscript; available in PMC 2021 August 01.

Published in final edited form as:

Clin Cancer Res. 2021 February 01; 27(3): 759–774. doi:10.1158/1078-0432.CCR-20-3396.

Regulation of CEACAM5 and therapeutic efficacy of an anti-CEACAM5-SN38 antibody-drug conjugate in neuroendocrine prostate cancer

Diana C. DeLucia[1], **Thomas M. Cardillo**[3], **Lisa Ang**[1], **Mark P. Labrecque**[5], **Ailin Zhang**[1], **James E. Hopkins**[1], **Navonil De Sarkar**[1], **Ilsa Coleman**[1], **Rui M. Gil da Costa**[1,2], **Eva Corey**[5], **Lawrence D. True**[6], **Michael C. Haffner**[1,2,6], **Michael T. Schweizer**[2,4], **Colm Morrissey**[5], **Peter S. Nelson**[1,2,4,5,6], **John K. Lee**[1,2,4,6,*]

[1]Human Biology Division, Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA

[2]Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA

[3]Immunomedics, Inc., Morris Plains, NJ 07950, USA

[4]Department of Medicine, University of Washington School of Medicine, Seattle, WA 98195, USA

[5]Department of Urology, University of Washington School of Medicine, Seattle, WA 98195, USA

[6]Department of Laboratory Medicine and Pathology, University of Washington School of Medicine, Seattle, WA 98195, USA

Abstract

Purpose: Neuroendocrine prostate cancer (NEPC) is an aggressive form of castration-resistant prostate cancer (CRPC) for which effective therapies are lacking. We previously identified carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5) as a promising NEPC cell surface antigen. Here we investigated the scope of CEACAM5 expression in end-stage prostate cancer, the basis for CEACAM5 enrichment in NEPC, and the therapeutic potential of the CEACAM5 antibody-drug conjugate labetuzumab govitecan in prostate cancer.

Experimental design: The expression of CEACAM5 and other clinically relevant antigens was characterized by multiplex immunofluorescence of a tissue microarray comprising metastatic tumors from 34 lethal mCRPC cases. A genetically defined neuroendocrine transdifferentiation assay of prostate cancer was developed to evaluate mechanisms of CEACAM5 regulation in NEPC. The specificity and efficacy of labetuzumab govitecan was determined in CEACAM5^{+} prostate cancer cell lines and patient-derived xenografts models.

*Corresponding author: John K. Lee, 1100 Fairview Ave N., E2-112, Seattle, WA 98109, 206-667-6819, jklee5@fredhutch.org.

Author contributions: D.C.D., T.M.C., M.T.S., and J.K.L. conceived and designed experiments. D.C.D, M.P.L., A.Z., L.A., and J.K.L. performed experiments. D.C.D., M.P.L., A.Z., J.E.H., N.D.S, I.C, R.M.G., L.D.T., and M.H., performed data analysis. E.C., C.M., and P.S.N. provided biological samples. D.C.D. and J.K.L. wrote the paper.

Conflict of interest statement: D.C.D. and J.K.L. received research funding from Immunomedics, Inc. T.M.C. was employed by Immunomedics, Inc., and holds stock or stock options in Immunomedics. Inc.

Data and material availability: Raw and analyzed RNA-seq and ATAC-seq data are available at GEO accession number GSE154576. All other materials will be available upon request and completion of a Material Transfer Agreement.

Results: CEACAM5 expression was enriched in NEPC compared to other mCRPC subtypes and minimally overlapped with PSMA, PSCA, and Trop2 expression. We focused on a correlation between the expression of the pioneer transcription factor *ASCL1* and *CEACAM5* to determine that ASCL1 can drive neuroendocrine reprogramming of prostate cancer which is associated with increased chromatin accessibility of the *CEACAM5* core promoter and CEACAM5 expression. Labetuzumab govitecan induced DNA damage in CEACAM5^{+} prostate cancer cell lines and marked antitumor responses in CEACAM5^{+} CRPC xenograft models including chemotherapy-resistant NEPC.

Conclusions: Our findings provide insights into the scope and regulation of CEACAM5 expression in prostate cancer and strong support for clinical studies of labetuzumab govitecan for NEPC.

Keywords

labetuzumab govitecan; CEACAM5; ASCL1; pioneer transcription factor; neuroendocrine prostate cancer

Introduction:

While androgen deprivation therapy (ADT) is initially effective for the treatment of hormone-sensitive prostate adenocarcinoma (PRAD), resistance is inevitable and leads to a state known as castration-resistant prostate cancer (CRPC). CRPC is heterogeneous and comprises multiple molecular phenotypes that diverge from conventional PRAD and include neuroendocrine prostate cancer (NEPC) which is a high-grade, poorly differentiated, and lethal neuroendocrine carcinoma with no effective treatments. NEPC accounts for up to 20% of lethal metastatic CRPC (mCRPC) and exhibits rapid metastatic dissemination, loss of androgen receptor (AR) signaling, and expression of neuroendocrine differentiation markers. NEPC rarely arises *de novo* and primarily emerges from PRAD through a process of neuroendocrine transdifferentiation as an adaptive response to the selective pressure of ADT (1).

While an understanding of the determinants of neuroendocrine transdifferentiation of prostate cancer remains incomplete, several genetic alterations have been associated with progression to NEPC. These include loss of the tumor suppressor genes *RB1* and *TP53*, amplification or overexpression of *MYCN* and *AURKA*, and activation of the PI3K/AKT pathway (2,3). These genetic derangements are also common to poorly differentiated neuroendocrine cancers arising from other epithelial tissues including the lung. In genetically engineered mouse models, combined loss of *Rb1*, *Trp53*, and *Pten* in the prostate promotes the development of tumors displaying castration resistance, lineage plasticity, and a neuroendocrine cancer phenotype (4,5). Human prostate epithelial transformation models have also underscored the importance of these genetic perturbations in the initiation of NEPC (6,7). Yet neuroendocrine transdifferentiation does not appear to be an obligate outcome of these genetic events in human prostate cancer (8), indicating that other factors may be involved.

In general, NEPC represents an epigenetic cancer state distinct from PRAD with unique patterns of DNA methylation, chromatin accessibility, and epigenetic regulator expression (6,9,10). However, NEPC can vary in histologic appearance and neuroendocrine marker expression, likely due to molecular heterogeneity. Small-cell lung cancer (SCLC) shares many phenotypic characteristics with NEPC. Recently, four molecular subtypes of SCLC have been identified, of which two are marked by differential expression and activity of the pioneer neural basic helix-loop-helix transcription factors achaete-scute homologue 1 (ASCL1) and neurogenic differentiation factor 1 (NeuroD1) (11). In a mouse model of SCLC driven by *Rb1* and *Trp53* loss, *Ascl1* but not *Neurod1* was required for the initiation of SCLC (12). NeuroD1^{high} SCLC appears to progress from an ASCL1^{high} SCLC state through a process mediated by enhanced *MYC* expression (13). Given the biological parallels between SCLC and NEPC, these lineage-defining transcription factors may also be operative in NEPC.

The expression of cell surface proteins reflects specific cellular lineage programs in normal development and in cancer. The development of targeted therapies directed against prostate cancer cell surface antigens is an active area of research that must account for the heterogeneity of CRPC phenotypes reflecting diverse cancer differentiation states. Using a systematic approach, we previously identified expression of the human carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5, also known as CEA) in a large subset of NEPC (14). CEACAM5 is a cell surface protein that is upregulated in a variety of other human epithelial malignancies including colorectal cancer (15) and has been functionally associated with tumor differentiation, invasion, and metastasis (16,17). Multiple therapeutic approaches to target CEACAM5 in cancer are in development including vaccines, bispecific T cell engagers, chimeric antigen receptor T cell therapies, and antibody-drug conjugates (ADC). Labetuzumab govitecan (IMMU-130) is a CEACAM5 ADC composed of a humanized CEACAM5 monoclonal antibody named labetuzumab conjugated to the potent topoisomerase I inhibitor 7-ethyl-10-hydroxycamptothecin (SN-38) via a unique hydrolysable linker (CL2A) (18). SN-38 is the active metabolite of irinotecan which is commonly used as chemotherapy for colorectal and pancreatic cancer (19). Labetuzumab govitecan has demonstrated activity in preclinical models of colorectal cancer (18,20) as well as safety and potential efficacy in a phase I/II clinical trial in patients with treatment-refractory metastatic colorectal cancer (21). However, labetuzumab govitecan has yet to be evaluated in the treatment of prostate cancer.

Here we characterize CEACAM5 expression in end-stage mCRPC relative to other cell surface antigens that are the active clinical focus of diagnostic and therapeutic development. We investigate the molecular basis for CEACAM5 expression in NEPC and uncover insights into the cancer differentiation-specific regulation of CEACAM5. Lastly, we evaluate the antitumor activity of labetuzumab govitecan in preclinical models of CEACAM5^{+} CRPC, including NEPC, to justify the clinical investigation of this therapeutic agent in prostate cancer.

Materials and Methods:

Cell lines.

DU145 (Cat# DU-145, RRID:CVCL_0105), 22Rv1 (Cat# CRL-2505, RRID:CVCL_1045), C4–2B (Cat# CRL-3315, RRID:CVCL_4784), and NCI-H660 (Cat# CRL-5813, RRID:CVCL_1576) cell lines were purchased from the American Tissue Culture collection (ATCC; Manassas, VA) and LNCaP95 were a gift from Dr. Stephen R. Plymate (University of Washington). All cell lines were validated by short tandem repeat analysis after receipt. DU145, 22Rv1, C4–2B, and MSKCC EF1 (derived from the organoid line MSKCC-CaP4) were maintained in RPMI medium supplemented with 10% fetal bovine serum (FBS), 100 U/ml penicillin and 100 ug/ml streptomycin, and 4 mM GlutaMAX™. NCI-H660 cells were maintained in Advanced DMEM/F12 medium supplemented with B27, 4 mM GlutaMAX™, and 10 ng/ml recombinant human bFGF and EGF. Cell lines were cultured no more than three weeks after thawing prior to use in described experiments.

mIF of TMAs.

UW mCRPC TAN TMA (Prostate Cancer Biorepository Network) and FDA normal organ TMA (US Biomax Inc.) were used for mIF studies (Tables S1, S2, and S3). Slides were stained on a Leica BOND Rx stainer (Leica, Buffalo Grove, IL) using Leica Bond reagents for antigen retrieval, antibody stripping (Epitope Retrieval Solution 2), and rinsing after each step (Bond Wash Solution). A high stringency wash was performed after the secondary and tertiary applications using high-salt TBST solution (0.05 M Tris, 0.3 M NaCl, and 0.1% Tween-20, pH 7.2–7.6). Opal Polymer HRP Mouse plus Rabbit (PerkinElmer, Hopkington, MA) was used for all secondary applications.

H-scoring of CEACAM5 expression.

H-scores were generated from the CEACAM5 mIF data using the CytoNuclear LC v2.0.6 module and HALO software. Briefly, individual cells were classified as having negative, weak, moderate, or strong CEACAM5 staining and assigned intensity scores of 0, 1, 2, and 3, respectively. The intensity score ranges were defined based on CEACAM5 fluorescent intensity values as follows: 0 = 0 – positive CEACAM5 threshold value, 1 = threshold value – 25^{th} quartile median, 2 = 25^{th} quartile median – 75^{th} quartile median, and 3 = 75^{th} quartile median – maximum value reported. Intensity scores were then multiplied by the percentage of stained cells for a range of 0–300.

Serum CEA quantification.

Cryopreserved serum samples obtained at rapid autopsy or a patient visit prior to rapid autopsy were obtained from the UW TAN repository. CEA quantification was performed using a CLIA-licensed Carcinoembryonic Antigen ELISA test (University of Washington Research Testing Services).

Exome sequencing analysis.

Paired-end exome sequencing (NGS) was performed using Illumina HiSeq or Illumina NovaSeq on genomic DNA isolated from rapid autopsy tissue samples. Sequence reads were

aligned to the human reference genome hg19 using the BWA aligner (RRID:SCR_010910). GATK (RRID:SCR_001876) best practice was adopted to process all aligned BAM files. Germline and somatic mutation analyses were performed using HaplotypeCaller and Mutect2. All detected mutations were annotated using ANNOVAR hg19 (RRID:SCR_012821) and manual curation was performed before determination of pathogenicity. Copy number was derived following the standardized Sequenza pipeline (RRID:SCR_016662). All copy number calls were manually curated for potentially missed mid-sized structural aberrations (15–50 nt indels).

C4–2B neuroendocrine transdifferentiation assay.

C4–2B cells were seeded in 6-well tissue culture plates at a density of 10^5 cells per ml in 3 ml of RPMI medium supplemented with 10% fetal bovine serum (FBS), 100 U/ml penicillin and 100 ug/ml streptomycin, and 4 mM GlutaMAX™. Cells were transduced approximately 4–6 hours after seeding at a defined multiplicity-of-infection of 4 for each lentivirus. Seventy-two hours after transduction, cells were trypsinized, washed, and transferred to 100 mm tissue culture plates in 15 ml of Advanced DMEM/F12 medium supplemented with B27, 4 mM GlutaMAX™, and 10 ng/ml recombinant human bFGF and EGF. Media was replenished every 3–4 days. Cells were collected 11 days post-transduction for analysis.

ATAC sequencing.

Briefly, 50,000 cells were lysed in buffer containing NP-40, Tween-20, and digitonin. Nuclei were collected after centrifugation and transposed with Tn5 transposase for 30 minutes at 37°C. DNA was purified by MinElute Reaction Cleanup Kit (Qiagen) followed by PCR amplification to append indices/adapters, library purification, and quality control by Agilent TapeStation and library quantitation by qPCR. ATAC-seq libraries underwent paired-end 50 bp sequencing on an Illumina NovaSeq 6000. Raw reads were processed with the ENCODE ATAC-seq pipeline (22) for quality control, alignment by Bowtie 2 (RRID:SCR_005476), and peak calling by MACS2 (RRID:SCR_013291). Inferred transcription factor activity was determined by HINT-ATAC (23) using HOCOMOCO (RRID:SCR_005409) and JASPAR (RRID:SCR_003030) binding motifs.

ATAC quantitative PCR.

ATAC-qPCR targeting the *CEACAM5* core promoter peak was performed using ATAC libraries on the QuantStudio5 System (Thermo Fisher Scientific) with Applied Biosystems PowerUp SYBR Green Master Mix (Thermo Fisher Scientific). The mean cycle threshold (Ct) obtained for each promoter region was normalized to the *AK5* control primers (24).

Immunoblots.

Whole cell extracts were fractionated by SDS-PAGE and transferred to a nitrocellulose membrane using a transfer apparatus according to the manufacturer's instructions (Invitrogen). Membranes were blocked with 5% nonfat milk in PBST (DPBS + 0.5% Tween 20) for 30 minutes while shaking, then incubated with primary antibodies at 4°C for 16 hours. Membranes were washed three times for 5 minutes with PBST and incubated with horseradish peroxidase-conjugated anti-mouse or anti-rabbit secondary antibody for 1 hour

at room temperature. Blots were washed three times for 5 minutes each with PBST and developed with Immobilon™ Western Chemiluminescent HRP Substrate (MilliporeSigma) for three minutes at room temperature. Blot images were acquired with a ChemiDoc^{MP} Imaging System (Bio-Rad) or autoradiography film.

CEACAM5 surface protein detection by flow cytometry.

DU145, 22Rv1, and MSKCC EF1 cells were dissociated with Versene-EDTA (Thermo Fisher Scientific) into single cell suspensions. Cells were washed once with monoclonal antibody wash buffer (MW; PBS + 0.1% FBS + 0.1% sodium azide) then resuspended in 100 μl MW and 5 μl of anti-CEACAM5-APC or IgG isotype-APC per 10^6 cells and incubated at room temperature in the dark for 30 minutes. Cells were washed once with MW, resuspended in MW, acquired on a BD FACSCanto II (BD Biosciences), and analyzed with FlowJo (v10) (RRID:SCR_008520).

Labetuzumab cell surface binding.

DU145, 22Rv1, and MSKCC EF1 cell lines expressing empty vector or CEACAM5 vector were dissociated non-enzymatically with Versene-EDTA into single cell suspensions. Cells were washed once with PBS and resuspended in 100 ul of 1 ug/ml of h679 or labetuzumab (Immunomedics, Inc.) and incubated at 4°C on ice for 1 hour. Cells were then washed twice with PBS, incubated with an anti-human IgG- PE-Cy5 secondary antibody (Thermo Fisher Scientific) at 4°C on ice for 30 minutes, washed with PBS, acquired on a SH800 (Sony), and analyzed with FlowJo (v10).

γH2AX detection of dsDNA breaks.

DU145, 22Rv1, and MSKCC EF1 cells were dissociated non-enzymatically with Versene-EDTA (Thermo Fisher Scientific), washed with PBS, resuspended in PBS and prechilled on ice at 4°C for 20 minutes, followed by incubation with labetuzumab govitecan or h679-SN-38 (Immunomedics, Inc.), or SN-38 (Sigma) for 30 minutes on ice at 4°C. Cells were then washed six times with cold PBS, and cultured for 16 hours in culture media at 37°C. For extended SN-38 treated conditions, cells were cultured at 37°C in media containing SN-38 for 16 hours. Cells were then dissociated with trypsin 0.25%, washed with MW, fixed with BD Cytofixation Buffer (BD Biosciences), permeabilized with BD Phosflow Perm Buffer II (BD Biosciences), and stained with anti-γH2AX-BV421 or IgG isotype control, as per manufacturer's instructions. Cells were washed twice with MW, resuspended in MW, acquired on a BD FACSCanto II (BD Biosciences), and analyzed with FlowJo (v10).

SN-38 dose responses in prostate cancer cell lines.

DU145, 22Rv1, MSKCC EF1, and NCI-H660 cells were seeded at 5×10^3 cells (50 μl) per well in 96-well flat bottom, tissue culture treated, white plates (Corning). Cells were treated with serial dilutions of SN-38 (50 μl) in replicates of 8, diluted in appropriate culture media, at 37°C for 96 hours. Cell viability was determined using the CellTiter-Glo 2.0 Assay (Promega).

Immunohistochemistry of LuCaP PDX tumors.

Formalin-fixed, paraffin-embedded tissue sections were baked at 65°C for 1–2 hours, deparaffinized in xyline, and rehydrated in 100%, 95%, and 70% ethanol. Tissue sections were heated in antigen retrieval buffer (0.2 M citric acid and 0.2 M sodium citrate) within a pressure cooker followed by PBS wash. Tissue slices were blocked with 2.5% horse serum for 30 minutes and then incubated with primary antibody diluted in 2.5% horse serum overnight at 4°C. HRP was detected with ImmPRESS-HRP anti-mouse or anti-rabbit IgG peroxidase detection kits (Vector Laboratories) and staining was visualized with DAB peroxidase substrate (Dako). Tissue sections were counterstained with hematoxylin and dehydrated for mounting.

Mouse xenograft studies.

All animal care and studies were performed in accordance with an approved Fred Hutchinson Cancer Research Center Institutional Animal Care and Use Committee protocol and Comparative Medicine regulations. Six-week old, male NSG (NOD-SCID-IL2Rγ-null, RRID:BCBC_4142) mice were obtained from the Jackson Laboratory. 5×10^6 cells from each prostate cancer cell line were suspended in 100 μl of cold Matrigel (Corning) and implanted by injection subcutaneously into NSG mice. For LuCaP PDXs, a 1 mm^3 piece of prostate tumor tissue was surgically implanted subcutaneously into NSG mice. Mice were enrolled into a treatment arm when tumors reached 150 mm^3 and treated by intraperitoneal injection at the frequency and with the doses described. Labetuzumab govitecan and h679-SN-38 doses were prepared fresh through reconstitution with 0.9% preservative-free sodium chloride (McKesson Medical-Surgical). Cisplatin and etoposide (NIH Developmental Therapeutics Program, RRID:SCR_003057) were prepared and stored at room temperature and 4°C, respectively. Mice were monitored biweekly for tumor growth, weight, and body condition score. A complete response is defined as an undetectable tumor.

Complete blood counts and serum chemistries.

Retro-orbital bleeds yielding ~200 μl of blood were performed on mice prior to receiving the first dose at enrollment on day 0, as well as on days 14 and 28 of the study. Blood was collected into green top lithium heparin microcontainers (Becton Dickinson) and tested within 24 hours (Phoenix Labs, Seattle, WA).

Statistical methods.

All data are shown as mean ± SD. For sample sizes less than 40, normality testing was performed with the D'Agostino-Pearson test. For single comparisons, statistical analyses were performed using a two-sided Student's t-test. For multiple comparisons, statistical analyses were performed using ANOVA with Tukey's post hoc correction. Data not normally distributed were alternatively analyzed using a two-sided Kruskal-Wallis nonparametric test or Brown-Forsythe and Welch ANOVA with Games-Howell nonparametric post hoc correction. For correlation analysis, Pearson correlations or Spearman rank correlations were performed for normal and not normal data, respectively. Best fit curves were generated with linear regression modeling. Significance was defined as $p \leq 0.05$.

All studies were conducted in accordance with the ethical guidelines expressed in the World Medical Association Declaration of Helsinki.

Results:

Enrichment of CEACAM5 protein expression in NEPC

To examine CEACAM5 expression across phenotypic subtypes of advanced prostate cancer, we performed immunofluorescence (IF) staining on a clinically and histologically annotated tissue microarray (TMA) of lethal mCRPC tissues from 34 patients collected at rapid autopsy through the University of Washington Tissue Acquisition Necropsy (UW TAN) program (25). Two of 34 patient samples were excluded due to poor quality cores, allowing for the complete analysis of 32 patient tissues. Tissues were classified into four tumor subtypes based on immunohistochemical staining for androgen receptor (AR), prostate-specific antigen (PSA), chromogranin A (ChrA), and synaptophysin (SYP): 1) androgen receptor positive prostate cancer (ARPC: AR^+ or PSA^+, $ChrA^-$, and SYP^-); 2) neuroendocrine prostate cancer (NEPC: AR^- and PSA^-, $ChrA^+$ or SYP^+); 3) double-negative prostate cancer (DNPC: AR^-, PSA^-, $ChrA^-$, and SYP^-); or 4) amphicrine prostate cancer (AMPC: AR^+ or PSA^+ and $ChrA^+$ or SYP^+). Stromal regions of tissue cores were classified based on morphology (Figure 1A) and excluded from all analyses to focus on tumor parenchyma. Image analysis revealed that the overall level of CEACAM5 expression was heightened in NEPC based on fluorescence intensity (Figure 1 B) and that NEPC cores contained significantly more $CEACAM5^+$ cells (44% ± 39.6%) (Figure 1C). Integrated CEACAM5 H-scores (% cells stained x staining intensity) were substantially higher in NEPC (81 ± 87.5) (Figure 1D) compared to other prostate cancer subtypes.

CEACAM5 expressed on the surface of cells is often shed into the bloodstream and can be measured as serum CEA. Serum CEA is a common clinical cancer biomarker but has had a relatively limited role in the clinical management of prostate cancer. Elevation of serum CEA combined with neuroendocrine tumor marker expression has previously been reported as a clinical criterion for aggressive variant prostate cancer, a spectrum of prostate cancers including NEPC that are molecularly characterized by combined defects in *TP53*, *RB1*, and *PTEN* and respond poorly to AR-directed therapies (26). To explore the relationship between serum CEA levels and tumor CEACAM5 expression in lethal mCRPC subtypes, we assayed banked serum samples collected concurrently with tumor tissue from 18 of the 34 patients represented in the UW mCRPC TAN TMA. We found a significant correlation between serum CEA levels and tumor CEACAM5 expression (r=0.40) based on H-score (Figure 1E). The correlation appeared to be driven primarily by patients with NEPC compared to other mCRPC subsets (Figure S1, A and B) but subgroup analysis was not statistically significant potentially due to limited sample size. These data suggest that serum CEA could be a valuable adjunct clinical biomarker of NEPC and should be investigated further as a part of prospective clinical trials.

Genomic profiling of prostate cancer by next-generation sequencing has identified distinct molecular disease subtypes (27). We performed a limited exploratory analysis of whole exome sequencing of 38 prostate cancer tissues (17 $CEACAM5^+$ and 21 $CEACAM5^-$) from 28 of 34 patients represented on the UW mCRPC TAN TMA. Our analysis focused on a

subset of genes commonly altered in mCRPC including *RB1* and *TP53* and genes in the PI3K/AKT signaling pathway (Table S). Monoallelic or biallelic copy loss of *RB1*, *TP53*, and *PTEN* appeared to be equally common in CEACAM5$^+$ and CEACAM5$^-$ mCRPC tissues, at frequencies consistent with prior reports (8,28). Predicted functional mutations were observed in *RB1* and *TP53,* and the mutational frequency was similar in CEACAM5$^+$ and CEACAM5$^-$ tissues. Monoallelic or biallelic copy loss of *FOXO3*, *MAP3K7*, and *RRAGD* was enriched in CEACAM5$^+$ samples compared to CEACAM5$^-$ samples by a factor of two. *MAP3K7* loss has specifically been reported to promote the development of clinically aggressive prostate cancer, and is associated with AR loss and neuroendocrine differentiation (29).

As tissues were collected from multiple metastatic sites (Tables S1 and S2) and variable CEACAM5 expression was identified within tissues, we next characterized the intra-patient phenotypic heterogeneity of mCRPC in the NEPC samples from the UW mCRPC TAN cohort. Four of eight (50%) patients with NEPC had mixed disease based on the presence of additional histologic phenotypes at other tumor sites (Figure 1F). To evaluate CEACAM5 expression in the context of this intra-patient heterogeneity, we examined all cores from each of these eight NEPC patients. Five of eight patients (62.5%) were found to have CEACAM5$^+$ NEPC (Patients 2, 5, 6, 7, and 8). In these five cases, CEACAM5 expression was present at all NEPC tissue sites, albeit with variability in the frequency of CEACAM5$^+$ cells between sites (Figure 1F). Additionally, the metastatic samples within these five patients that lacked CEACAM5 expression exhibited non-NEPC phenotypes (Figure 1F). These data further demonstrate enhanced CEACAM5 expression in NEPC, not only across a diverse series of patients, but also within patients harboring phenotypically heterogeneous mCRPC.

We also profiled CEACAM5 expression by IF in a normal human organ TMA (Tables S1 and S3). Consistent with prior reports, CEACAM5 expression was detectable at low levels in multiple healthy tissues including the lung, stomach, small intestine, and colon (Figure S2, A–C) (14,30,31). However, the intensity of CEACAM5 staining in normal organs was significantly lower than in NEPC samples represented in the UW mCRPC TAN TMA (Figure 1D). This difference in expression could signify a therapeutic window for agents directed at CEACAM5 when applied to NEPC. Collectively, these results provide a comprehensive assessment of CEACAM5 expression in patients with lethal mCRPC, including NEPC, and in healthy human tissues.

CEACAM5 expression relative to other targetable cell surface antigens in prostate cancer

Multiple clinically relevant prostate cancer antigens including trophoblast cell surface antigen 2 (Trop2), prostate-specific membrane antigen (PSMA), and prostate stem cell antigen (PSCA) are the focus of intense clinical development for mCRPC. The Trop2-directed ADC sacituzumab govitecan (IMMU-132) is currently being evaluated in a phase II study for mCRPC (32). PSMA bispecific T cell engagers, PSMA radioligand therapies, and PSMA and PSCA chimeric antigen receptor T cell therapies are also under clinical investigation for mCRPC. We focused on characterizing the co-expression of CEACAM5 and these prostate cancer antigens in lethal mCRPC using a multiplex IF (mIF) staining

panel on the UW mCRPC TAN TMA (Figure S3). mIF image analysis demonstrated inverse patterns of 1) CEACAM5 and 2) Trop2, PSMA, and PSCA staining frequencies and intensities in NEPC and ARPC tissue cores (Figure 2, A and B). Specifically, CEACAM5 expression was enriched in NEPC while Trop2, PSMA, and PSCA expression was heightened in ARPC. Further, PSMA and PSCA were frequently expressed in Trop2^{+} cores in ARPC but not in NEPC, DNPC, or AMPC (Figure 2C). These results are consistent with the prior characterization of Trop2 as an epithelial marker and the established androgen-regulated nature of PSMA and PSCA expression (33,34). In contrast, Trop2, PSMA, and PSCA were much less frequently expressed in CEACAM5^{+} cores in NEPC (Figure 2D).

We evaluated mIF data at a single-cell level across all ARPC and NEPC tissue cores to investigate more granular, digital relationships between 1) Trop2, PSMA, and PSCA co-expression in ARPC and 2) CEACAM5, Trop2, PSMA, and PSCA co-expression in NEPC. Trop2 and PSMA (r=0.42) but not PSCA (r=0.01) expression were correlated in ARPC cells (Figure 2E). On the other hand, CEACAM5 did not correlate with Trop2 (r=0) or PSMA (r=0.13) and weakly correlated with PSCA (r=0.27) expression in NEPC cells (Figure 2F). The variable co-expression of Trop2, PSMA, and/or PSCA indicate the presence of highly heterogeneous ARPC cell populations in lethal mCRPC. Further, these findings suggest that diagnostic and therapeutic modalities under investigation to target Trop2, PSMA, and PSCA in prostate cancer may not effectively localize and treat CEACAM5^{+} NEPC.

Association between ASCL1 and CEACAM5 expression in NEPC

CEACAM5 is highly expressed in colorectal cancer where prior studies have implicated transforming growth factor beta (TGF-β) and retinoic acid signaling in *CEACAM5* transcriptional regulation (35,36). However, little is known about the regulation of *CEACAM5* expression in other cancer types including NEPC. Based on published literature, we discovered that CEACAM5 is expressed in some neuroendocrine carcinomas such as medullary thyroid carcinoma (MTC) and SCLC but not others like Merkel cell carcinoma (37,38). MTC arises from parafollicular cells which represent calcitonin-secreting neuroendocrine cells of the thyroid that require ASCL1 for their development (39). In SCLC, *CEACAM5* expression is specifically enriched in the ASCL1^{high} subtype over other subtypes including NeuroD1^{high} SCLC (Figure S4, A and B). In contrast, Merkel cell carcinoma does not express ASCL1 and instead uniformly expresses NeuroD1 (37,40).

Based on these associations in other neuroendocrine carcinomas, we postulated that ASCL1 may regulate CEACAM5 expression in NEPC. To explore this possibility, we first examined the two available cell line models of NEPC, NCI-H660 and MSKCC EF1. Previously, we have shown that NCI-H660 cells express CEACAM5 and MSKCC EF1 cells do not (14). Transcriptome profiling revealed differential enrichment of *ASCL1* in NCI-H660 and *NEUROD1* in MSKCC EF1 cells (Figure 3A), consistent with our hypothesis. We further examined gene expression data from Stand Up To Cancer (SU2C) mCRPC biopsies (41), UW mCRPC TAN rapid autopsies (42), and the LuCaP patient-derived xenograft (PDX) series (42) to scrutinize *CEACAM5*, *ASCL1*, and *NEUROD1* expression in NEPC. Across these three datasets, *CEACAM5* expression generally associated with *ASCL1* expression but not *NEUROD1* expression in NEPC samples (Figure 3B). In the SU2C dataset, *CEACAM5*

expression was strongly correlated with *ASCL1* (r=0.95), but not *NEUROD1* (r=0.12) across mCRPC samples demonstrating a neuroendocrine score of >0.4 consistent with NEPC (Figure 3, C and E). The Beltran 2016 NEPC cohort (9) also showed a positive correlation for *CEACAM5* and *ASCL1* (r=0.75) and interestingly *NEUROD1* to a lesser extent (r=0.44) (Figure 3, D and F). The correlation between *ASCL1* and *NEUROD1* expression was negative (r=−0.27) in the SU2C dataset while the same comparison showed a positive correlation (r=0.39) in the Beltran dataset (Figure 3, G and H). These findings may reflect increased representation of mixed ASCL1^{high} and NeuroD1^{high} NEPC tumors in the Beltran dataset. Of note, Delta-like 3 (DLL3) is a Notch ligand enriched in NEPC (43) that is the target of multiple therapeutics in clinical development for SCLC and is known to be regulated by ASCL1 (44). *CEACAM5* expression correlated with *DLL3* expression in the SU2C (r=0.54) and Beltran 2016 NEPC (r=0.46) datasets (Figure S5, A and B), suggesting that both genes might be regulated by similar programs.

Regulation of CEACAM5 expression during neuroendocrine transdifferentiation of prostate cancer

To uncover possible cis-regulatory elements involved in the transcriptional regulation of *CEACAM5* in prostate cancer, we examined chromatin accessibility of the *CEACAM5* gene locus using Assay for Transposase-Accessible Chromatin using sequencing (ATAC-seq) in multiple prostate cancer cell lines, including the NEPC cell lines NCI-H660 and MSKCC EF1 and the AR^{+} cell lines 22Rv1 and LNCaP95. We identified a differential chromatin accessibility peak located at −191 to −92 upstream of the *CEACAM5* transcriptional start site encompassing FANTOM5 Cap Analysis of Gene Expression (CAGE) tags of promoter elements in the CEACAM5^{+} NCI-H660 cell line but not in the CEACAM5^{-} MSKCC EF1, 22Rv1, or LNCaP95 cell lines (Figure 4A). This peak overlaps with the previously described core promoter region spanning −403 to −124 of the *CEACAM5* gene locus *(45)* and was also prominent in pan-cancer The Cancer Genome Atlas (TCGA) ATAC-seq data (46) in tumor types where CEACAM5 is expressed including colorectal (COAD), esophageal (ESCA), gastric (STAD), and breast cancer (BRCA) (Figure 4A). Consistent with these findings, a coinciding DNase I hypersensitivity site was observed in CEACAM5^{+} normal colon tissues but not in CEACAM5^{-} normal breast tissues analyzed by the Encyclopedia of DNA Elements (ENCODE) Project (Figure S6). In addition, the peak heights of the DNase I hypersensitivity site corresponded to reported levels of CEACAM5 expression in colorectal and breast cancer cell lines (Figure S6).

Inferred transcription factor binding from ATAC-seq indicated enhanced activity of ASCL1 in NCI-H660 cells and NeuroD1 in MSKCC EF1 cells (Figure 4B) which is in concert with their differential expression in these cell lines. However, functional validation studies with short hairpin RNA (shRNA)-mediated knockdown of ASCL1 in NCI-H660 cells and ectopic expression of ASCL1 in MSKCC EF1 cells had no discernable effect on CEACAM5 expression (Figure 4C). ASCL1 and NeuroD1 knockdown in the respective NCI-H660 and MSKCC EF1 cells lines was detrimental to cell viability compared to controls (Figure S7, A–C), indicating perhaps that these lines are genetically hardwired and intolerant of perturbations to these transcription factors. The data could also imply that ASCL1 may not regulate CEACAM5 expression through direct transactivation. To corroborate this idea, we

examined published ASCL1 chromatin immunoprecipitation followed by sequencing (ChIP-seq) data across multiple studies from ASCL1^{high} SCLC cell lines (12,47,48), including the NCI-H889 and NCI-H1755 cell lines which express outlier levels of CEACAM5 (Figure S8A). These analyses indicate the absence of ASCL1 binding peaks near the *CEACAM5* gene locus (Figure S8B) but the presence of previously characterized peaks associated with genes bound by ASCL1 such as *DLL3* and *BCL2 (12,44)* (Figure S8, C and D). We therefore hypothesized that ASCL1, as a pioneer neural transcription factor, may epigenetically regulate *CEACAM5* by chromatin remodeling. We also reasoned that genetic studies in the hardwired NCI-H660 and MSKCC EF1 NEPC cell lines may not recapitulate dynamic epigenetic regulation of *CEACAM5* expression that occurs during the progression of human prostate cancer.

As an alternative approach, we developed a genetically defined system to induce neuroendocrine transdifferentiation of prostate cancer. We introduced *ASCL1* and other factors causally associated with neuroendocrine transdifferentiation of prostate cancer including dominant-negative *TP53* R175H, shRNA targeting *RB1* (shRb1), and *MYCN* either alone or in combination into the androgen-independent ARPC cell line C4–2B. While C4–2B cells do not express CEACAM5 at baseline, we discovered that all conditions in which *ASCL1* was introduced stimulated expression of CEACAM5 and the neuroendocrine markers synaptophysin (SYP) and insulinoma-associated protein 1 (INSM1) (Figure 4D). In contrast, all other C4–2B conditions in which *ASCL1* was omitted did not exhibit neuroendocrine differentiation (Figure 4D). We discovered that ectopic expression of NeuroD1 within this system also induced CEACAM5, SYP, and INSM1 expression (Figure 4E). Notably, expression of ASCL1 and/or NeuroD1 downregulated AR and AR-dependent NK3 homeobox 1 (NKX3–1) expression (Figure 4E), indicating that these factors may be critical in orchestrating lineage reprogramming from ARPC to NEPC. We also observed that overexpression of NeuroD1 induced ASCL1 expression and the introduction of both ASCL1 and NeuroD1 further enhanced CEACAM5 expression (Figure 4E).

We evaluated a second ASCL family member, ASCL2, in the C4–2B cell line to determine whether these effects may be specific to ASCL1. ASCL2 is also a pioneer transcription factor involved in the specification of multiple lineages including trophectoderm (49), T-helper cells (50), and intestinal stem cells (51). Further, ASCL2 expression is associated with the non-neuroendocrine POU2F3^{high} variant subtype of SCLC (52) and is enriched in multiple cancer types where CEACAM5 is commonly expressed (Figure S9, A–C). Enforced expression of *ASCL2*, in combination with *TP53* R175H, shRB1, and *MYCN*, in C4–2B cells suppressed AR and NKX3–1 expression, but did not upregulate CEACAM5, SYP, or INSM1 expression (Figure 4F). These data emphasize the differential competence of pioneer transcription factors to effect neuroendocrine transdifferentiation of prostate cancer and induce CEACAM5 expression within this system.

To investigate the epigenetic regulation of the core promoter of *CEACAM5* in our C4–2B functional studies, we developed ATAC-quantitative polymerase chain reaction (qPCR) assays incorporating universal normalization control primers targeting *AK5* and three unique primer pairs targeting the differential chromatin accessible and DNase I hypersensitive site we identified in the core promoter of *CEACAM5*. The assays were validated using ATAC

libraries generated from the NCI-H660 and MSKCC EF1 cell lines (Figure 4G). C4–2B cells reprogrammed with ASCL1 revealed a five-fold enhancement in chromatin accessibility at the core promoter of *CEACAM5* relative to control conditions (Figure 4H). In contrast, no increase in chromatin accessibility was associated with ASCL2 and only a minor, non-significant increase was associated with NeuroD1 (Figure 4H). These results point to one mechanism by which neuroendocrine transdifferentiation driven by ASCL1 may be epigenetically linked to CEACAM5 expression in prostate cancer.

In vitro specificity and cytotoxicity of labetuzumab govitecan in NEPC

We previously reported that a CEACAM5 chimeric antigen receptor T cell therapy demonstrates antitumor activity in NEPC cell line models (14). However, we recognized the lengthy time horizon and numerous hurdles to advancing this type of cancer treatment to the clinic. We therefore concentrated on studies to target CEACAM5 in prostate cancer by redirecting the established CEACAM5 ADC labetuzumab govitecan with the anticipation that compelling results could lead to an accelerated path to clinical translation. We first characterized the specific binding of labetuzumab, the humanized antibody component of labetuzumab govitecan, to prostate cancer cell lines with native and engineered expression of CEACAM5. CEACAM5 was stably expressed in three CEACAM5$^-$ prostate cancer cell lines: the AR$^+$ line 22Rv1, the AR$^-$ line DU145, and the NEPC line MSKCC EF1 (Figure 5A). We detected labetuzumab binding in all four cell lines expressing CEACAM5 as well as the natively CEACAM5$^+$ NCI-H660 cell line, but not in isogenic negative control cell lines (Figure 5B).

We then investigated the genotoxic effects of labetuzumab govitecan on the prostate cancer cell line panel by measuring γH2AX, a marker of double-stranded DNA (dsDNA) breaks. Cells were incubated with labetuzumab govitecan for 30 minutes, extensively washed to remove unbound drug, and propagated in cell culture for 16 hours prior to staining and analysis. Labetuzumab govitecan provoked greater γH2AX signal in the CEACAM5$^+$ 22Rv1 cell line relative to the control 22Rv1 cell line and compared to incubation with the non-specific ADC, h679-SN-38 (Figure 5C). In contrast, SN-38 alone induced γH2AX in an antigen-independent manner in both the CEACAM5$^+$ and CEACAM5$^-$ 22Rv1 cell lines (Figure 5C). H679-SN-38, labetuzumab govitecan, and SN-38 did not generate substantial γH2AX signal in the DU145 and MSKCC EF1 cell lines, irrespective of CEACAM5 expression status (Figure 5, D and E). To determine the overall susceptibility of the cell lines to SN-38, we assessed γH2AX levels following a longer exposure to SN-38 in culture. After a 16 hour incubation, SN-38 induced γH2AX in all three cell lines (Figure S10, A–C), albeit to different extents consistent with drug sensitivity based on IC_{50} calculations from dose-response curves in each of the cell lines with the exception of DU145 (Figure S10D). These data confirm the specificity of labetuzumab binding and the genotoxicity of labetuzumab govitecan in CEACAM5$^+$ prostate cancer cell lines which generally correlates with the relative sensitivities of the lines to SN-38.

In vivo antitumor activity of labetuzumab govitecan in NEPC

We first examined the antitumor activity of labetuzumab govitecan *in vivo* using CEACAM5$^+$ NCI-H660 NEPC cell line xenograft tumors established in NOD-*scid IL2rγ*^{null}

(NSG) mice. Mice were treated with labetuzumab govitecan, h679-SN-38, or vehicle by intraperitoneal injections weekly for a total of four treatments over 28 days. By day 17 and day 24, 100% of tumors in the labetuzumab govitecan treatment arm (n=10) and the h679-SN-38 arm (n=9) were undetectable, respectively (Figure S11A). In contrast, tumors in the vehicle treatment arm demonstrated uncontrolled growth (Figure S11A). No significant changes in mouse weight (Figure S11B) or body condition score (Figure S11C) were observed throughout the study at the 25 mg/kg dose. Four of nine (45%) vehicle-treated mice were sacrificed prior to completion of the study as they exceeded institutional tumor size restrictions (Figure S11D).

We next tested labetuzumab govitecan treatment in multiple LuCaP PDXs established from lethal mCRPC tissues (53) that express varying levels of CEACAM5. The LuCaP 49 and LuCaP 145.1 NEPC PDXs were classified as CEACAM5$^{low/moderate}$ and CEACAM5^{high} expression models, respectively, based on intensity of immunohistochemical staining (Figure S12). Mice were treated with labetuzumab govitecan or h679-SN-38 at 25 mg/kg or vehicle by intraperitoneal injection every four days. Complete responses were observed in 100% of labetuzumab govitecan (n=10) and h679-SN-38-treated mice (n=8) bearing LuCaP 49 PDX tumors by day 14 (Figure 6A). Complete responses were also observed in 100% of labetuzumab govitecan-treated mice (n=8) with LuCaP 145.1 PDX tumors by day 14, while h679-SN-38 treatment suppressed tumor growth but did not eradicate tumors in any mice (Figure 6B). Importantly, the LuCaP 49 and LuCaP 145.1 tumor models were relatively resistant to cisplatin and etoposide chemotherapy (Figure 6, A and B) which is considered the standard-of-care frontline treatment for extensive stage NEPC.

In the LuCaP 49 study, the average weight loss in the labetuzumab govitecan group comparing treatment pre-enrollment to day 28 was 10%. However, this weight loss occurred within the first week of treatment and weights otherwise remained stable in all groups for the remainder of the study (Figure S13A). Additionally, no significant changes in body condition scores were observed (Figure S13A). No significant changes in weight or body condition score were observed in mice in the LuCaP 145.1 study (Figure S13B). Adverse effects on liver and kidney function are often reported in association with irinotecan chemotherapy. We performed serum chemistries on days 0, 14, and 28 to assess for these and other toxicities (Figure S14A). Across both studies, three of 18 (17%) labetuzumab govitecan-treated mice exhibited elevated aspartate aminotransferase (AST) levels at day 28 that were less than twice the upper limit of the reference range (Figure S14, B and C), indicating mild hepatotoxicity in these animals. Complete blood counts were also performed (Figure S14D). Across both studies, six of 18 (33%) labetuzumab govitecan-treated mice exhibited leukocytosis at day 28 (Figure S14E) with an increase in the neutrophil fraction (Figure S14F). Similar results were observed in the h679-SN-38 and cisplatin and etoposide-treated mice compared to vehicle-treated mice (Figure S14D).

Given the striking antitumor effects but mild toxicities associated with labetuzumab govitecan at the 25 mg/kg dose, we tested labetuzumab govitecan at a reduced dose with less frequent dosing. NSG mice bearing CEACAM5$^{low/moderate}$ LuCaP 49 NEPC PDX tumors or CEACAM5^{high} LuCaP 176 AR^{low}/NE^{-} PDX tumors were treated with labetuzumab govitecan or h679-SN-38 at 25 mg/kg or 12.5 mg/kg by intraperitoneal injection weekly. In

the LuCaP 49 model, both dose levels of labetuzumab govitecan led to complete responses in 100% of mice (n=7) by day 21. While both dose levels of h679-SN-38 inhibited tumor growth, only the 25 mg/kg dose led to tumor eradication (Figure 6C). The LuCaP 176 model displayed more of a dose-dependent treatment response compared to LuCaP 49. The 25 mg/kg dose of labetuzumab govitecan led to complete responses in 100% of mice (n=6) by day 17. In contrast, tumor eradication was observed in three of six (50%) of mice treated with 12.5 mg/kg of labetuzumab govitecan (Figure 6D). Both dose levels of h679-SN-38 slowed tumor growth but did not diminish tumor volume. No significant changes in weight or body condition score were detected for either study (Figure S13, C and D). These studies highlight the potency and efficacy of labetuzumab govitecan in CEACAM5^{+} prostate cancer PDX models by demonstrating that a reduced dose and administration schedule are also capable of achieving complete responses.

Discussion:

The development and translation of safe and effective new therapies for NEPC are necessary to alter the course of this highly aggressive and deadly disease. The identification of tumor-restricted cell surface antigens and their targeting with antibodies, ADCs, or adoptive cell therapies has yet to make a clinical impact on the management of NEPC. Recent, substantial efforts have focused on targeting the ASCL1-regulated Notch ligand DLL3, but advanced clinical development of the promising DLL3-targeting ADC rovalpituzumab tesirine was discontinued due to excessive toxicity likely related to the pyrrolobenzodiazepine dimer payload (54). Our work indicates that CEACAM5 is a compelling cell surface antigen for therapeutic targeting in NEPC as it is expressed in over 60% of NEPC across multiple cohorts of patients, including those with end-stage disease, and demonstrates limited systemic expression. To accelerate therapeutic development, we redirected the existing CEACAM5-targeted ADC, labetuzumab govitecan, currently being evaluated for metastatic colorectal cancer, to NEPC. In multiple preclinical studies, labetuzumab govitecan treatment of patient-derived CEACAM5-expressing tumors resulted in complete responses. Labetuzumab govitecan is similar in design to the ADC sacituzumab govitecan, which was recently approved for the treatment of metastatic triple-negative breast cancer and has received fast-track designation for metastatic urothelial carcinoma and non-small cell lung cancer. Labetuzumab govitecan and sacituzumab govitecan share the same unique hydrolyzable linker, as well as SN-38 as the cytotoxic payload, and have collectively demonstrated manageable toxicities in patients across several clinical studies (21,55,56).

Our studies examining the expression of CEACAM5 and other relevant cell surface antigens in a large cohort of lethal mCRPC samples provide significant biological insights and have important clinical implications. We identified a correlation between serum CEA levels and CEACAM5 expression in tumor tissues across a small series of end-stage mCRPC patients, which appears most prominent in cases of NEPC. The measurement of serum CEA in the appropriate prostate cancer context (e.g. disease progression with a low prostate-specific antigen) might have value for diagnostic and/or therapeutic purposes in the identification, treatment selection, and disease monitoring of patients with CEACAM5^{+} NEPC. Further investigation of serum CEA as a biomarker in clinical trials for NEPC will be necessary to determine its utility. While expression of Trop2, PSMA, and PSCA has been reported to be

relatively homogeneous in early stages of prostate cancer, our results indicate that there is significant heterogeneity in their expression in end-stage mCRPC. Our results show that CEACAM5 expression marks a biologically distinct subset of prostate cancer that has relatively minor overlap with Trop2, PSMA, or PSCA expression. The clinical implication is that CEACAM5^{+} NEPC will not be detected by emerging imaging modalities and may be impervious to treatment approaches directed at Trop2, PSMA, or PSCA.

We also established the functional relevance of ASCL1 and NeuroD1 expression in driving neuroendocrine lineage reprogramming of prostate cancer. These transcription factors appear to induce a simultaneous reduction in AR expression, AR-dependent NKX3–1 expression, and the acquisition of neuroendocrine differentiation markers. Global epigenetic reprogramming of prostate cancer induced by these pioneer transcription factors may coordinately silence the AR-enforced epithelial cancer program and engender neuroendocrine cancer programs. Studies are underway to characterize the contributions of ASCL1 and NeuroD1 to the process of neuroendocrine transdifferentiation of prostate cancer through the integration of genetic, transcriptomic, and epigenetic approaches. Our findings indicate that the biology of NEPC may parallel that of SCLC in that they share ASCL1^{high} and NeuroD1^{high} disease subtypes. However, whether the tuft cell variant POU2F3^{high} or YAP1^{high} subtypes found in SCLC (11) also exist in NEPC has yet to be determined. A recent publication suggests potential biological divergence of NEPC from SCLC in that YAP1 expression is de-enriched in NEPC compared to other subsets of mCRPC (57).

A mechanistic understanding of the regulation of CEACAM5 expression and its specificity to certain cancers has generally been lacking. Previous studies have shown that the wide-ranging modulation of cancer cell differentiation states by retinoic acid or sodium butyrate treatment impacts CEACAM5 expression (36). Our work demonstrates that ASCL1 promotes neuroendocrine transdifferentiation of prostate cancer which results in increased chromatin accessibility of the core promoter of *CEACAM5*. We suspect that this mechanism of *CEACAM5* regulation by ASCL1 may be conserved in other neuroendocrine carcinomas including SCLC, but additional functional studies will be necessary for confirmation. An interesting question arising from our findings is whether additional pioneer transcription factors may similarly modulate the epigenomes of other tumor types to permit CEACAM5 expression in non-neuroendocrine cancer cell contexts.

The diversity of prostate cancer phenotypes that emerge with castration-resistance and their coexistence in late-stage patients indicate that single-targeted therapies may be ineffective. The existence of multiple subtypes of NEPC that may impact expression of target antigens like CEACAM5 and DLL3 in NEPC further compound this issue. Targeted prostate cancer therapies with multiple mechanisms of action or combinations of treatments may be necessary to conquer such diversity. Our *in vivo* studies demonstrate strong antitumor activity of labetuzumab govitecan and, to a lesser extent, the non-specific h679-SN-38 ADC which is likely a consequence of linker hydrolysis and systemic release of SN-38. Labetuzumab govitecan therefore represents a monotherapy that delivers both regional, antigen-specific and systemic, non-specific tumor killing. The benefit of a moderately stable ADC linker may be increased efficacy in patients with inter- and intra-tumoral heterogeneity,

such as that observed in cases of mixed NEPC which occurs in up to 50% of cases. This bystander effect has also been demonstrated in a number of other tumor types for the sister molecule sacituzumab govitecan (58,59).

The results of these studies have led to planning for a forthcoming phase I/II clinical trial of labetuzumab govitecan for patients with CEACAM5^{+} NEPC. CEACAM5 is also expressed in other neuroendocrine carcinomas including SCLC and MTC. More than half of SCLC are ASCL1^{high} (11) with the majority expressing CEACAM5, while advanced MTC are almost uniformly ASCL1^{high} and express CEACAM5 (38). Investigation of whether labetuzumab govitecan is effective in these and other CEACAM5^{+} neuroendocrine carcinomas may also be warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

We would like to first and foremost thank the patients and their families for their contributions, without which this research would not have been possible. We acknowledge Celestia Higano, Evan Yu, Heather Cheng, Bruce Montgomery, Elahe Mostaghel, Andrew Hsieh, Daniel Lin, Funda Vakar-Lopez, Xiaotun Zhang, Martine Roudier, Lawrence True, and the rapid autopsy teams for their contributions to the University of Washington Medical Center Prostate Cancer Donor Rapid Autopsy Program. We also thank Serengulam Govindan (Immunomedics, Inc.) for his constructive review of the manuscript. Additionally, we thank Fred Hutch Comparative Medicine for their support and assistance with animal trials, as well as Fred Hutch Experimental Histopathology for their assistance with mIF acquisition and analysis.

Funding: This work was funded by a Department of Defense Prostate Cancer Research Program Awards W81XWH-17-1-0129 (J.K. Lee), W81XWH-18-1-0347 (P.S. Nelson, C. Morrissey), Prostate Cancer Foundation Challenge Award (J.K. Lee), and Immunomedics, Inc. D.C. DeLucia is supported by a Department of Defense Prostate Cancer Research Program Early Investigator Research Award W81XWH-20-1-0119 and a Movember Foundation-Prostate Cancer Foundation Challenge Award. J. K. Lee is also supported by Department of Defense W81XWH-19-1-0758 and W81XWH19-1-0569, a Movember Foundation-Prostate Cancer Foundation Challenge Award, NIH 2P50CA092131 and 5P50CA097186, and Swim Across America. N. De Sarkar is supported by a Department of Defense Prostate Cancer Research Program Early Investigator Research Award W81XWH-17-1-0380. The tissue collection, analysis, and xenograft development was supported by the Department of Defense Prostate Cancer Biorepository Network (PCBN) Award W81XWH-14-2-0183 (C. Morrissey, E. Corey, L.D. True), Idea Development Award-Partnering-PI W81XWH-17-1-0414 (C. Morrissey, P.S. Nelson); W81XWH-17-1-0415, the Pacific Northwest Prostate Cancer SPORE award P50CA97186 (P.S. Nelson), an NIH PO1 award PO1 CA163227 (E. Corey, L.D. True, C. Morrissey), the Richard M. LUCAS Foundation, and the Institute for Prostate Cancer Research (IPCR).

References:

1. Beltran H, Hruszkewycz A, Scher HI, Hildesheim J, Isaacs J, Yu EY, et al. The Role of Lineage Plasticity in Prostate Cancer Therapy Resistance. Clinical cancer research : an official journal of the American Association for Cancer Research 2019;25(23):6916–24 doi 10.1158/1078-0432.Ccr-19-1423. [PubMed: 31363002]
2. Beltran H, Rickman DS, Park K, Chae SS, Sboner A, MacDonald TY, et al. Molecular characterization of neuroendocrine prostate cancer and identification of new drug targets. Cancer Discov 2011;1(6):487–95 doi 10.1158/2159-8290.CD-11-0130. [PubMed: 22389870]
3. Tan HL, Sood A, Rahimi HA, Wang W, Gupta N, Hicks J, et al. Rb loss is characteristic of prostatic small cell neuroendocrine carcinoma. Clin Cancer Res 2014;20(4):890–903 doi 10.1158/1078-0432.CCR-13-1982. [PubMed: 24323898]

4. Zhou Z, Flesken-Nikitin A, Corney DC, Wang W, Goodrich DW, Roy-Burman P, et al. Synergy of p53 and Rb deficiency in a conditional mouse model for metastatic prostate cancer. Cancer Res 2006;66(16):7889–98 doi 10.1158/0008-5472.CAN-06-0486. [PubMed: 16912162]

5. Ku SY, Rosario S, Wang Y, Mu P, Seshadri M, Goodrich ZW, et al. Rb1 and Trp53 cooperate to suppress prostate cancer lineage plasticity, metastasis, and antiandrogen resistance. Science 2017;355(6320):78–83 doi 10.1126/science.aah4199. [PubMed: 28059767]

6. Park JW, Lee JK, Sheu KM, Wang L, Balanis NG, Nguyen K, et al. Reprogramming normal human epithelial tissues to a common, lethal neuroendocrine cancer lineage. Science 2018;362(6410):91–5 doi 10.1126/science.aat5749. [PubMed: 30287662]

7. Lee JK, Phillips JW, Smith BA, Park JW, Stoyanova T, McCaffrey EF, et al. N-Myc Drives Neuroendocrine Prostate Cancer Initiated from Human Prostate Epithelial Cells. Cancer Cell 2016;29(4):536–47 doi 10.1016/j.ccell.2016.03.001. [PubMed: 27050099]

8. Nyquist MD, Corella A, Coleman I, De Sarkar N, Kaipainen A, Ha G, et al. Combined TP53 and RB1 Loss Promotes Prostate Cancer Resistance to a Spectrum of Therapeutics and Confers Vulnerability to Replication Stress. Cell Rep 2020;31(8):107669 doi 10.1016/j.celrep.2020.107669. [PubMed: 32460015]

9. Beltran H, Prandi D, Mosquera JM, Benelli M, Puca L, Cyrta J, et al. Divergent clonal evolution of castration-resistant neuroendocrine prostate cancer. Nat Med 2016;22(3):298–305 doi 10.1038/nm.4045. [PubMed: 26855148]

10. Clermont PL, Lin D, Crea F, Wu R, Xue H, Wang Y, et al. Polycomb-mediated silencing in neuroendocrine prostate cancer. Clinical epigenetics 2015;7:40 doi 10.1186/s13148-015-0074-4. [PubMed: 25859291]

11. Rudin CM, Poirier JT, Byers LA, Dive C, Dowlati A, George J, et al. Molecular subtypes of small cell lung cancer: a synthesis of human and mouse model data. Nat Rev Cancer 2019;19(5):289–97 doi 10.1038/s41568-019-0133-9. [PubMed: 30926931]

12. Borromeo MD, Savage TK, Kollipara RK, He M, Augustyn A, Osborne JK, et al. ASCL1 and NEUROD1 Reveal Heterogeneity in Pulmonary Neuroendocrine Tumors and Regulate Distinct Genetic Programs. Cell Rep 2016;16(5):1259–72 doi 10.1016/j.celrep.2016.06.081. [PubMed: 27452466]

13. Mollaoglu G, Guthrie MR, Bohm S, Bragelmann J, Can I, Ballieu PM, et al. MYC Drives Progression of Small Cell Lung Cancer to a Variant Neuroendocrine Subtype with Vulnerability to Aurora Kinase Inhibition. Cancer Cell 2017;31(2):270–85 doi 10.1016/j.ccell.2016.12.005. [PubMed: 28089889]

14. Lee JK, Bangayan NJ, Chai T, Smith BA, Pariva TE, Yun S, et al. Systemic surfaceome profiling identifies target antigens for immune-based therapy in subtypes of advanced prostate cancer. Proc Natl Acad Sci U S A 2018;115(19):E4473–E82 doi 10.1073/pnas.1802354115. [PubMed: 29686080]

15. Blumenthal RD, Leon E, Hansen HJ, Goldenberg DM. Expression patterns of CEACAM5 and CEACAM6 in primary and metastatic cancers. BMC Cancer 2007;7:2 doi 10.1186/1471-2407-7-2. [PubMed: 17201906]

16. Hashino J, Fukuda Y, Oikawa S, Nakazato H, Nakanishi T. Metastatic potential of human colorectal carcinoma SW1222 cells transfected with cDNA encoding carcinoembryonic antigen. Clin Exp Metastasis 1994;12(4):324–8 doi 10.1007/BF01753839. [PubMed: 8039306]

17. Powell E, Shao J, Picon HM, Bristow C, Ge Z, Peoples M, et al. A functional genomic screen in vivo identifies CEACAM5 as a clinically relevant driver of breast cancer metastasis. NPJ Breast Cancer 2018;4:9 doi 10.1038/s41523-018-0062-x. [PubMed: 29736411]

18. Govindan SV, Cardillo TM, Moon SJ, Hansen HJ, Goldenberg DM. CEACAM5-targeted therapy of human colonic and pancreatic cancer xenografts with potent labetuzumab-SN-38 immunoconjugates. Clin Cancer Res 2009;15(19):6052–61 doi 10.1158/1078-0432.CCR-09-0586. [PubMed: 19789330]

19. Weekes J, Lam AK, Sebesan S, Ho YH. Irinotecan therapy and molecular targets in colorectal cancer: a systemic review. World J Gastroenterol 2009;15(29):3597–602 doi 10.3748/wjg.15.3597. [PubMed: 19653336]

20. Govindan SV, Cardillo TM, Rossi EA, Trisal P, McBride WJ, Sharkey RM, et al. Improving the therapeutic index in cancer therapy by using antibody-drug conjugates designed with a moderately cytotoxic drug. Mol Pharm 2015;12(6):1836–47 doi 10.1021/mp5006195. [PubMed: 25402018]

21. Dotan E, Cohen SJ, Starodub AN, Lieu CH, Messersmith WA, Simpson PS, et al. Phase I/II Trial of Labetuzumab Govitecan (Anti-CEACAM5/SN-38 Antibody-Drug Conjugate) in Patients With Refractory or Relapsing Metastatic Colorectal Cancer. J Clin Oncol 2017;35(29):3338–46 doi 10.1200/JCO.2017.73.9011. [PubMed: 28817371]

22. Jinwook Lee DK, Grey Cristoforo, Chuan-Sheng Foo, Chris Probert, Nathan Beley, & Anshul Kundaje. . ENCODE ATAC-seq pipeline (Version 1.5.4). Zenodo 2019 doi 10.5281/zenodo.3564813.

23. Li Z, Schulz MH, Look T, Begemann M, Zenke M, Costa IG. Identification of transcription factor binding sites using ATAC-seq. Genome Biol 2019;20(1):45 doi 10.1186/s13059-019-1642-2. [PubMed: 30808370]

24. Yost KE, Carter AC, Xu J, Litzenburger U, Chang HY. ATAC Primer Tool for targeted analysis of accessible chromatin. Nat Methods 2018;15(5):304–5 doi 10.1038/nmeth.4663. [PubMed: 29702633]

25. Roudier MP, True LD, Higano CS, Vesselle H, Ellis W, Lange P, et al. Phenotypic heterogeneity of end-stage prostate carcinoma metastatic to bone. Hum Pathol 2003;34(7):646–53 doi 10.1016/s0046-8177(03)00190-4. [PubMed: 12874759]

26. Aparicio AM, Harzstark AL, Corn PG, Wen S, Araujo JC, Tu SM, et al. Platinum-based chemotherapy for variant castrate-resistant prostate cancer. Clin Cancer Res 2013;19(13):3621–30 doi 10.1158/1078-0432.CCR-12-3791. [PubMed: 23649003]

27. Cancer Genome Atlas Research N. The Molecular Taxonomy of Primary Prostate Cancer. Cell 2015;163(4):1011–25 doi 10.1016/j.cell.2015.10.025. [PubMed: 26544944]

28. Quigley DA, Dang HX, Zhao SG, Lloyd P, Aggarwal R, Alumkal JJ, et al. Genomic Hallmarks and Structural Variation in Metastatic Prostate Cancer. Cell 2018;174(3):758–69 e9 doi 10.1016/j.cell.2018.06.039. [PubMed: 30033370]

29. Rodrigues LU, Rider L, Nieto C, Romero L, Karimpour-Fard A, Loda M, et al. Coordinate loss of MAP3K7 and CHD1 promotes aggressive prostate cancer. Cancer Res 2015;75(6):1021–34 doi 10.1158/0008-5472.CAN-14-1596. [PubMed: 25770290]

30. Klaile E, Klassert TE, Scheffrahn I, Muller MM, Heinrich A, Heyl KA, et al. Carcinoembryonic antigen (CEA)-related cell adhesion molecules are co-expressed in the human lung and their expression can be modulated in bronchial epithelial cells by non-typable Haemophilus influenzae, Moraxella catarrhalis, TLR3, and type I and II interferons. Respir Res 2013;14:85 doi 10.1186/1465-9921-14-85. [PubMed: 23941132]

31. Terada T An immunohistochemical study of primary signet-ring cell carcinoma of the stomach and colorectum: III. Expressions of EMA, CEA, CA19–9, CDX-2, p53, Ki-67 antigen, TTF-1, vimentin, and p63 in normal mucosa and in 42 cases. Int J Clin Exp Pathol 2013;6(4):630–8. [PubMed: 23573309]

32. Lang JM, Kyriakopoulos C, Slovin SF, Eickhoff JC, Dehm S, Tagawa ST. Single-arm, phase II study to evaluate the safety and efficacy of sacituzumab govitecan in patients with metastatic castration-resistant prostate cancer who have progressed on second generation AR-directed therapy. 2020;38(6_suppl):TPS251–TPS doi 10.1200/JCO.2020.38.6_suppl.TPS251.

33. Jain A, Lam A, Vivanco I, Carey MF, Reiter RE. Identification of an androgen-dependent enhancer within the prostate stem cell antigen gene. Mol Endocrinol 2002;16(10):2323–37 doi 10.1210/me.2002-0004. [PubMed: 12351697]

34. Wright GL Jr., Grob BM, Haley C, Grossman K, Newhall K, Petrylak D, et al. Upregulation of prostate-specific membrane antigen after androgen-deprivation therapy. Urology 1996;48(2):326–34 doi 10.1016/s0090-4295(96)00184-7. [PubMed: 8753752]

35. Han SU, Kwak TH, Her KH, Cho YH, Choi C, Lee HJ, et al. CEACAM5 and CEACAM6 are major target genes for Smad3-mediated TGF-beta signaling. Oncogene 2008;27(5):675–83 doi 10.1038/sj.onc.1210686. [PubMed: 17653079]

36. Niles RM, Wilhelm SA, Thomas P, Zamcheck N. The effect of sodium butyrate and retinoic acid on growth and CEA production in a series of human colorectal tumor cell lines representing

different states of differentiation. Cancer Invest 1988;6(1):39–45 doi 10.3109/07357908809077027. [PubMed: 3365571]

37. Corella AN, Cabiliza Ordonio MVA, Coleman I, Lucas JM, Kaipainen A, Nguyen HM, et al. Identification of Therapeutic Vulnerabilities in Small-cell Neuroendocrine Prostate Cancer. Clin Cancer Res 2020;26(7):1667–77 doi 10.1158/1078-0432.CCR-19-0775. [PubMed: 31806643]
38. Mendelsohn G, Wells SA Jr., Baylin SB. Relationship of tissue carcinoembryonic antigen and calcitonin to tumor virulence in medullary thyroid carcinoma. An immunohistochemical study in early, localized, and virulent disseminated stages of disease. Cancer 1984;54(4):657–62 doi 10.1002/1097-0142(1984)54:4<657::aid-cncr2820540412>3.0.co;2-v. [PubMed: 6378353]
39. Lanigan TM, DeRaad SK, Russo AF. Requirement of the MASH-1 transcription factor for neuroendocrine differentiation of thyroid C cells. J Neurobiol 1998;34(2):126–34. [PubMed: 9468384]
40. Chteinberg E, Sauer CM, Rennspiess D, Beumers L, Schiffelers L, Eben J, et al. Neuroendocrine Key Regulator Gene Expression in Merkel Cell Carcinoma. Neoplasia 2018;20(12):1227–35 doi 10.1016/j.neo.2018.10.003. [PubMed: 30414538]
41. Abida W, Cyrta J, Heller G, Prandi D, Armenia J, Coleman I, et al. Genomic correlates of clinical outcome in advanced prostate cancer. Proc Natl Acad Sci U S A 2019;116(23):11428–36 doi 10.1073/pnas.1902651116. [PubMed: 31061129]
42. Labrecque MP, Coleman IM, Brown LG, True LD, Kollath L, Lakely B, et al. Molecular profiling stratifies diverse phenotypes of treatment-refractory metastatic castration-resistant prostate cancer. J Clin Invest 2019;130:4492–505 doi 10.1172/JCI128212.
43. Puca L, Gavyert K, Sailer V, Conteduca V, Dardenne E, Sigouros M, et al. Delta-like protein 3 expression and therapeutic targeting in neuroendocrine prostate cancer. Sci Transl Med 2019;11(484) doi 10.1126/scitranslmed.aav0891.
44. Nelson BR, Hartman BH, Ray CA, Hayashi T, Bermingham-McDonogh O, Reh TA. Acheate-scute like 1 (Ascl1) is required for normal delta-like (Dll) gene expression and notch signaling during retinal development. Dev Dyn 2009;238(9):2163–78 doi 10.1002/dvdy.21848. [PubMed: 19191219]
45. Hauck W, Stanners CP. Transcriptional regulation of the carcinoembryonic antigen gene. Identification of regulatory elements and multiple nuclear factors. J Biol Chem 1995;270(8):3602–10 doi 10.1074/jbc.270.8.3602. [PubMed: 7876096]
46. Corces MR, Granja JM, Shams S, Louie BH, Seoane JA, Zhou W, et al. The chromatin accessibility landscape of primary human cancers. Science 2018;362(6413) doi 10.1126/science.aav1898.
47. Augustyn A, Borromeo M, Wang T, Fujimoto J, Shao C, Dospoy PD, et al. ASCL1 is a lineage oncogene providing therapeutic targets for high-grade neuroendocrine lung cancers. Proc Natl Acad Sci U S A 2014;111(41):14788–93 doi 10.1073/pnas.1410419111. [PubMed: 25267614]
48. Hokari S, Tamura Y, Kaneda A, Katsura A, Morikawa M, Murai F, et al. Comparative analysis of TTF-1 binding DNA regions in small-cell lung cancer and non-small-cell lung cancer. Mol Oncol 2020;14(2):277–93 doi 10.1002/1878-0261.12608. [PubMed: 31782890]
49. Bogutz AB, Oh-McGinnis R, Jacob KJ, Ho-Lau R, Gu T, Gertsenstein M, et al. Transcription factor ASCL2 is required for development of the glycogen trophoblast cell lineage. PLoS Genet 2018;14(8):e1007587 doi 10.1371/journal.pgen.1007587. [PubMed: 30096149]
50. Liu X, Chen X, Zhong B, Wang A, Wang X, Chu F, et al. Transcription factor achaete-scute homologue 2 initiates follicular T-helper-cell development. Nature 2014;507(7493):513–8 doi 10.1038/nature12910. [PubMed: 24463518]
51. van der Flier LG, van Gijn ME, Hatzis P, Kujala P, Haegebarth A, Stange DE, et al. Transcription factor achaete scute-like 2 controls intestinal stem cell fate. Cell 2009;136(5):903–12 doi 10.1016/j.cell.2009.01.031. [PubMed: 19269367]
52. Huang YH, Klingbeil O, He XY, Wu XS, Arun G, Lu B, et al. POU2F3 is a master regulator of a tuft cell-like variant of small cell lung cancer. Genes Dev 2018;32(13–14):915–28 doi 10.1101/gad.314815.118. [PubMed: 29945888]
53. Zhang X, Coleman IM, Brown LG, True LD, Kollath L, Lucas JM, et al. SRRM4 Expression and the Loss of REST Activity May Promote the Emergence of the Neuroendocrine Phenotype in

Castration-Resistant Prostate Cancer. Clin Cancer Res 2015;21(20):4698–708 doi 10.1158/1078-0432.CCR-15-0157. [PubMed: 26071481]

54. Poirier JT. IA24 Targeting DLL3 in Small-Cell Lung Cancer with Novel Modalities. Journal of Thoracic Oncology 2020;15(2):S8 doi 10.1016/j.jtho.2019.12.024.
55. Bardia A, Mayer IA, Diamond JR, Moroose RL, Isakoff SJ, Starodub AN, et al. Efficacy and Safety of Anti-Trop-2 Antibody Drug Conjugate Sacituzumab Govitecan (IMMU-132) in Heavily Pretreated Patients With Metastatic Triple-Negative Breast Cancer. J Clin Oncol 2017;35(19):2141–8 doi 10.1200/JCO.2016.70.8297. [PubMed: 28291390]
56. Bardia A, Mayer IA, Vahdat LT, Tolaney SM, Isakoff SJ, Diamond JR, et al. Sacituzumab Govitecan-hziy in Refractory Metastatic Triple-Negative Breast Cancer. N Engl J Med 2019;380(8):741–51 doi 10.1056/NEJMoa1814213. [PubMed: 30786188]
57. Cheng S, Prieto-Dominguez N, Yang S, Connelly ZM, StPierre S, Rushing B, et al. The expression of YAP1 is increased in high-grade prostatic adenocarcinoma but is reduced in neuroendocrine prostate cancer. Prostate Cancer Prostatic Dis 2020 doi 10.1038/s41391-020-0229-z.
58. Perrone E, Lopez S, Zeybek B, Bellone S, Bonazzoli E, Pelligra S, et al. Preclinical Activity of Sacituzumab Govitecan, an Antibody-Drug Conjugate Targeting Trophoblast Cell-Surface Antigen 2 (Trop-2) Linked to the Active Metabolite of Irinotecan (SN-38), in Ovarian Cancer. Front Oncol 2020;10:118 doi 10.3389/fonc.2020.00118. [PubMed: 32117765]
59. Zeybek B, Manzano A, Bianchi A, Bonazzoli E, Bellone S, Buza N, et al. Cervical carcinomas that overexpress human trophoblast cell-surface marker (Trop-2) are highly sensitive to the antibody-drug conjugate sacituzumab govitecan. Sci Rep 2020;10(1):973 doi 10.1038/s41598-020-58009-3. [PubMed: 31969666]

Statement of Translational Relevance:

Neuroendocrine prostate cancer (NEPC) is an aggressive subtype of castration-resistant prostate cancer without effective treatments. Here we examined the expression of CEACAM5 compared to other relevant prostate cancer antigens in a series of lethal, metastatic prostate cancers. CEACAM5 is preferentially expressed in NEPC and tumor expression appears to correlate with serum CEA levels in NEPC cases. Through functional genomics studies, we illustrate the potential role of the pioneer transcription factor ASCL1 in the epigenetic regulation of CEACAM5 expression and neuroendocrine transdifferentiation of prostate cancer. Lastly, we redirect the anti-CEACAM5-SN38 antibody-drug conjugate, labetuzumab govitecan, for preclinical studies in prostate cancer and demonstrate tumor eradication in multiple xenograft models of CEACAM5^{+} prostate cancer including NEPC. Overall, we describe the scope of CEACAM5 expression in end-stage prostate cancer, report a mechanism of CEACAM5 gene regulation by ASCL1, and provide evidence to support imminent clinical investigation of labetuzumab govitecan in men with CEACAM5^{+} NEPC.

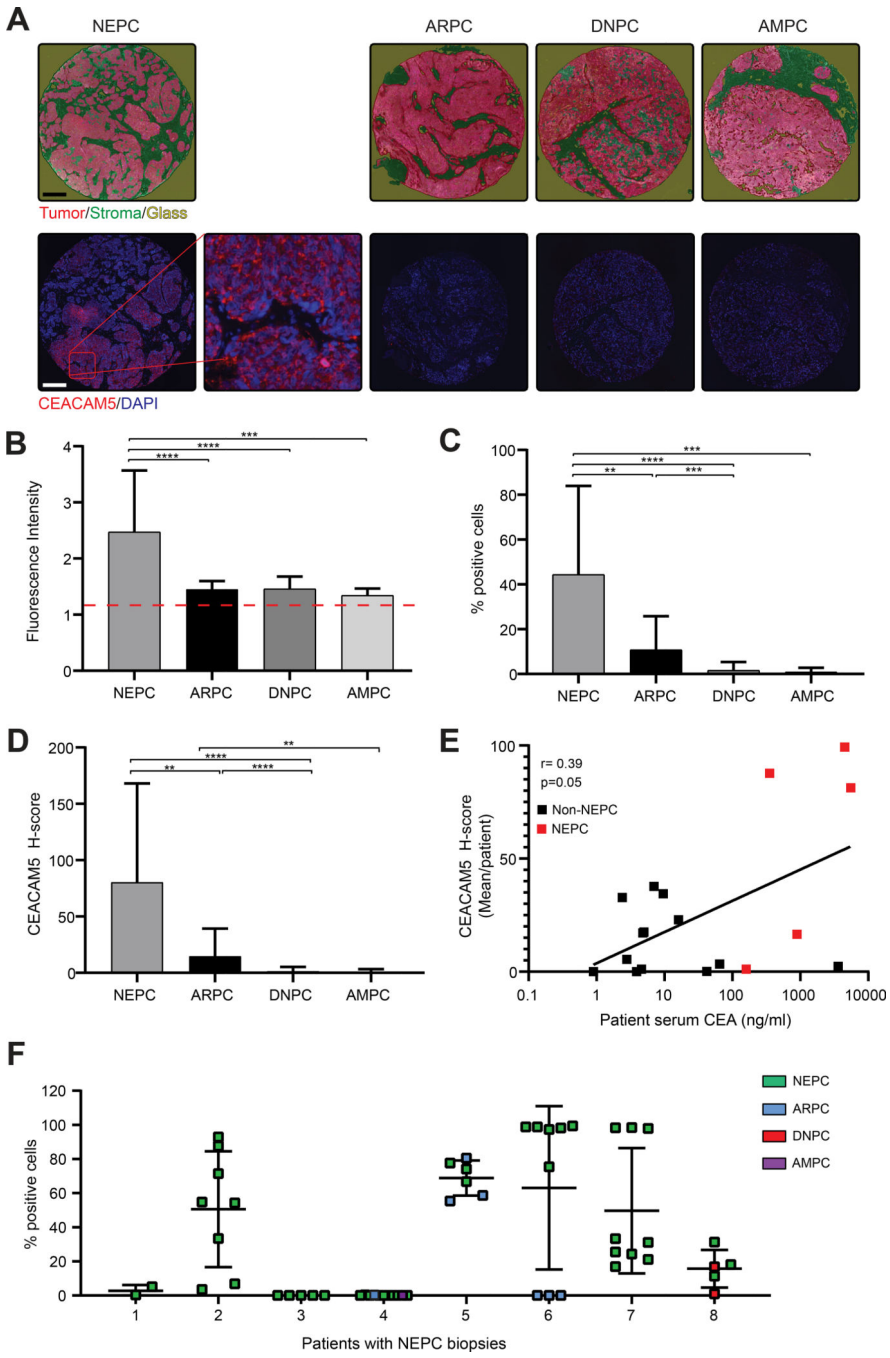


Figure 1. CEACAM5 expression is enriched in the NEPC subtype of mCRPC.

(A) Representative TMA images of individual cores with tumor and stroma annotation as well as fluorescent CEACAM5 (red) and nuclear DAPI (blue) staining (scale bars, 200 μm; original magnification, 20X). (B) Intensity of CEACAM5 staining, (C) percentage of cells with CEACAM5 expression, and (D) H-scores of neuroendocrine (NEPC, n=20), androgen receptor positive (ARPC, n=70), double-negative (DNPC, n=14), and amphicrine (AMPC, n=3) prostate cancers tissue samples. (E) CEA levels in mCRPC patient serum correlated to relative CEACAM5 protein expression (mIF H-score) in corresponding NEPC (n=5) and

non-NEPC (ARPC or DNPC) (n=13) patient tumor samples. CEA normal range: 0–5.0 ng/ml. (F) CEACAM5^{+} cell percentage within the tumor region of cores from all UW mCRPC TAN TMA patient donors with at least one NEPC classified biopsy core. Histograms depict mean + SD. ** p<0.01; *** p<0.001; **** p<0.0001. Red Dash = CEACAM5 staining intensity positive threshold. r=correlation coefficient. Kruskal-Wallis p values are shown for plots C and D. Spearman rank correlation coefficient (r) and p value is shown for plot E.

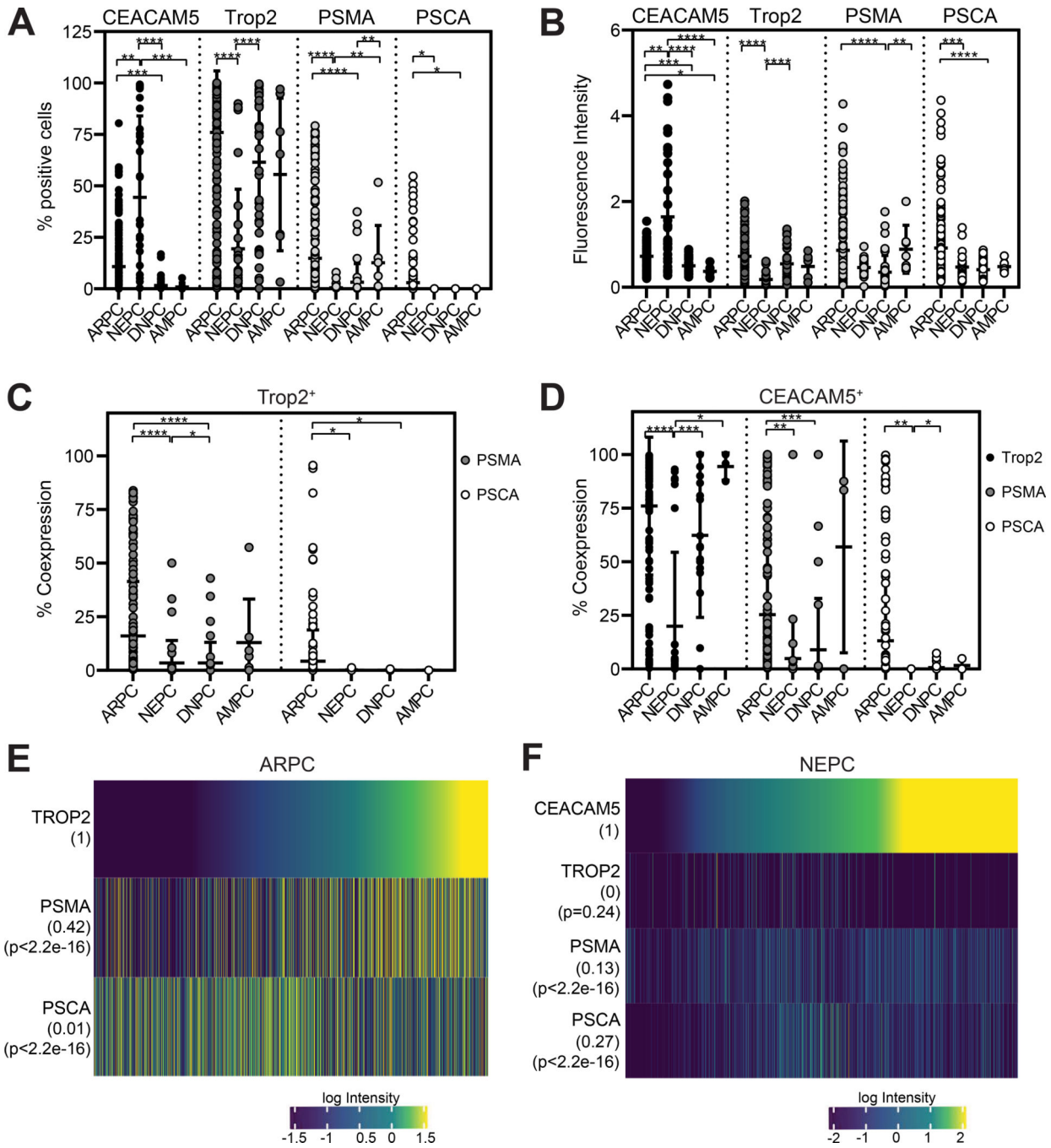


Figure 2. CEACAM5 expression relative to other targetable prostate cancer cell surface antigens.

(A) Percentage of cells expressing CEACAM5, Trop2, PSMA, and PSCA, and (B) staining intensity from mIF of ARPC (n=70), NEPC (n=20), DNPC (n=14), and AMPC (n=3) tissue cores. (C) Co-expression of PSMA and PSCA in Trop2^{+} cells per core. (D) Co-expression of Trop2, PSMA, and PSCA in CEACAM5^{+} cells per core. (E) Quantitative single-cell mIF signal intensities of proteins (rows) in cells from ARPC (n=655,676) and (F) NEPC cores (n=113,509). Error bars represent ± SD. * p<0.05; ** p<0.01; *** p<0.001; **** p<0.0001.

Kruskal-Wallis p values are shown for plots A-D. Pearson correlation coefficient (r) and P values for each measured protein is shown numerically next to heatmap rows.

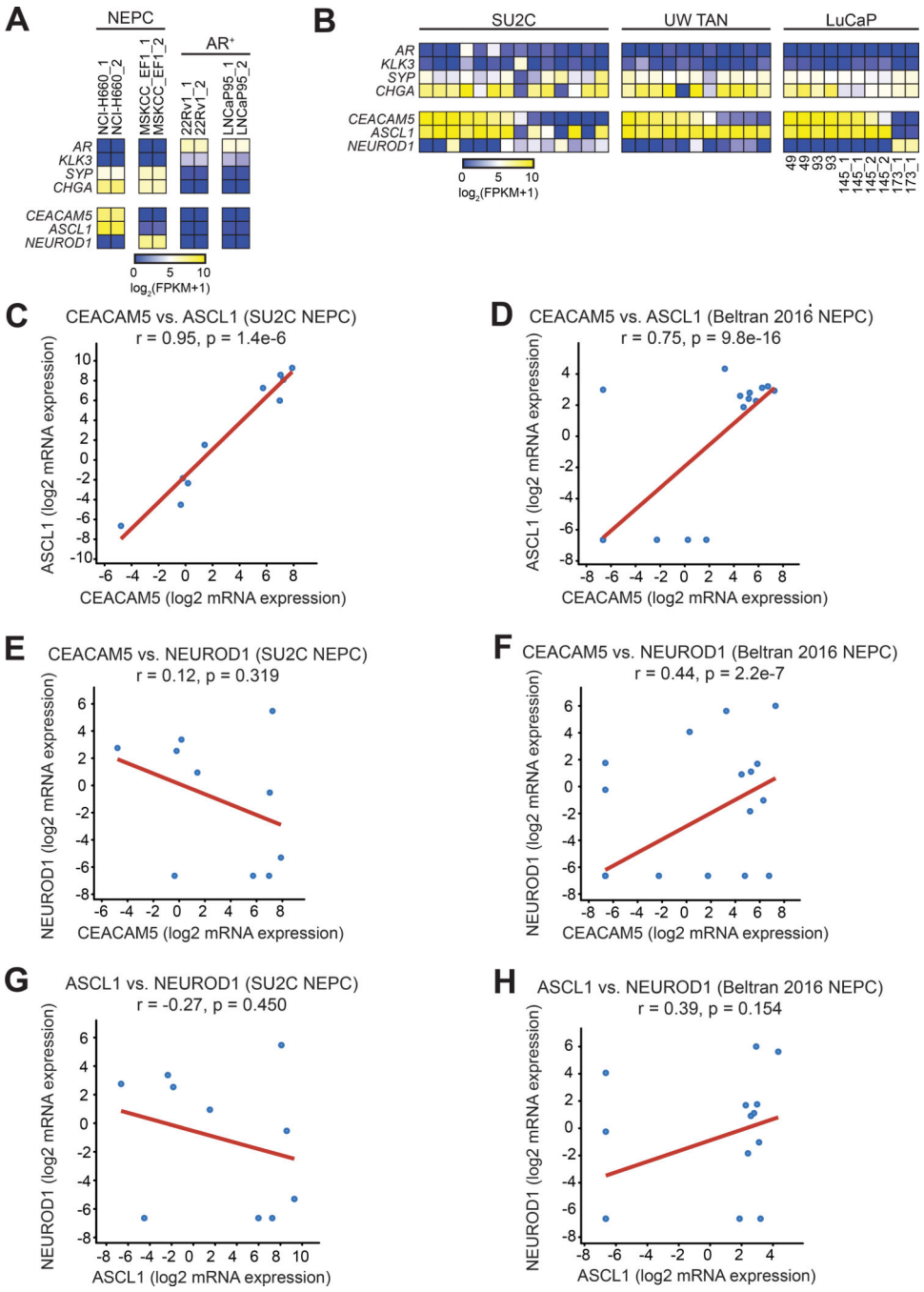


Figure 3. Association of ASCL1 and CEACAM5 expression in NEPC.

(A) RNA-seq gene expression heatmap of *ASCL1* and *NEUROD1* in NCI-H660, MSKCC EF1, 22Rv1, and LNCaP95 cell lines. (B) RNA-seq gene expression heatmap of NEPC samples (columns) from the Stand Up To Cancer (SU2C) mCRPC cohort, the University of Washington Tissue Acquisition Necropsy (UW TAN) lethal mCRPC cohort, and LuCaP patient-derived xenograft lines. (C-D) Correlation dot plots of CEACAM5 and ASCL1, (E-F) CEACAM5 and NEUROD1, and (G-H) ASCL1 and NEUROD1 gene expression in NEPC samples defined by a neuroendocrine gene signature score >0.4 in the SU2C dataset

(n=10) and the Beltran 2016 NEPC dataset (n=15). Pearson correlation coefficients (r) are shown for correlative gene expression analyses.

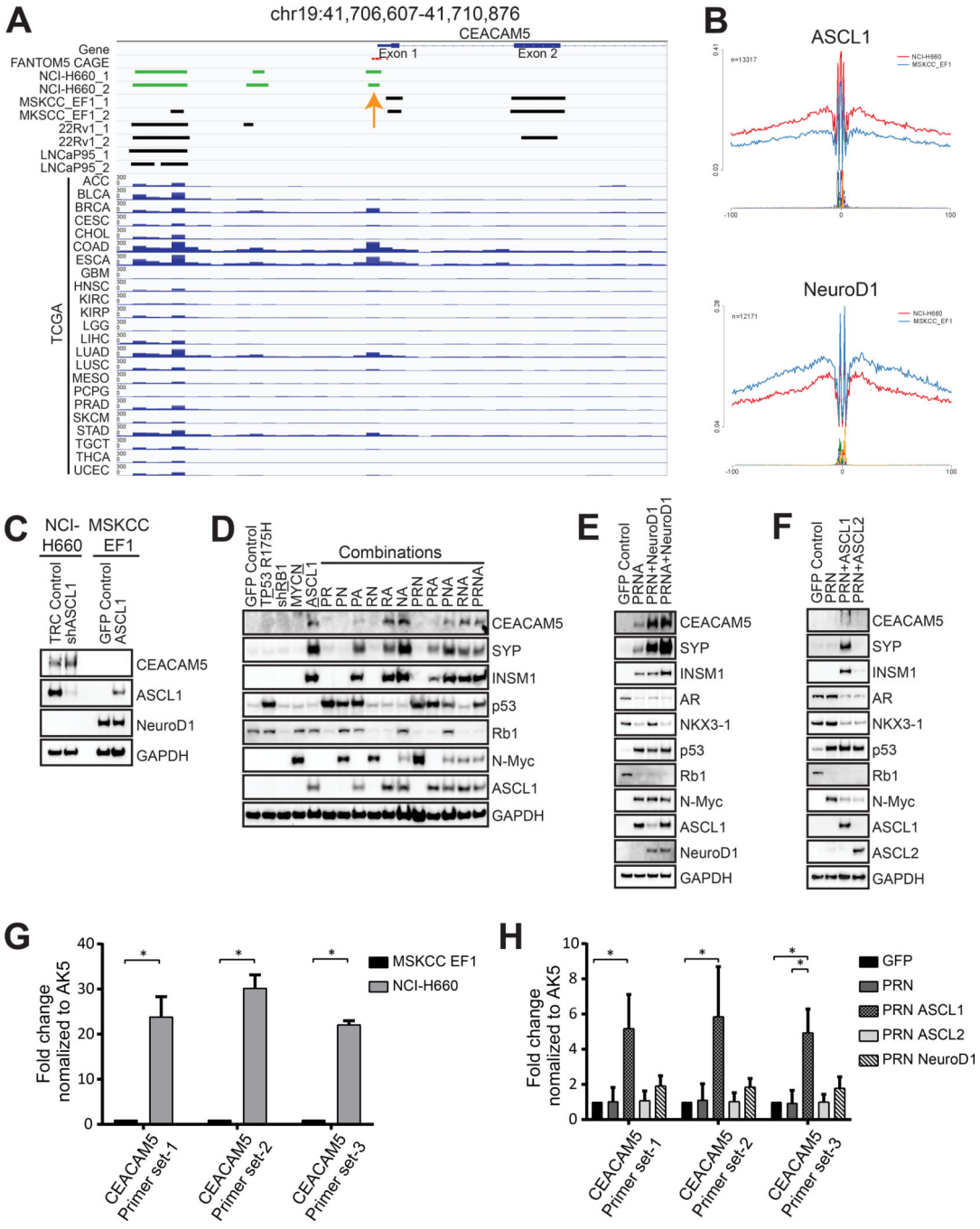


Figure 4. Regulation of CEACAM5 expression during neuroendocrine transdifferentiation.

(A) Integrative Genomics Viewer tracks showing an ATAC-seq peak at the promoter (orange arrow) upstream of the transcriptional start site of *CEACAM5*. (B) Lineplots demonstrating inferred ASCL1 and NeuroD1 activity in the NCI-H660 and MSKCC EF1 cell lines using differential transcription factor binding motif footprinting of ATAC-seq data. (C) Immunoblots demonstrating CEACAM5 protein expression in NCI-H660 cells with ASCL1 knockdown by shRNA and in MSKCC EF1 cells with ectopic ASCL1 expression. (D) Immunoblots showing CEACAM5 and neuroendocrine differentiation marker expression in

C4–2B cells overexpressing ASCL1, (E) NeuroD1, or (F) ASCL2 in the context of p53 R175H, Rb1 knockdown, and/or overexpression of N-Myc. Chromatin accessibility of the *CEACAM5* promotor determined by ATAC-qPCR in (G) NCI-H660 cells relative to MSKCC EF1 cells and (H) C4–2B control cells and cells reprogrammed with ASCL1, ASCL2, or NeuroD1. P=p53 R175H; R=shRB1; N=N-Myc; A=ASCL1. Histograms depict means + SD for biological replicates each with two technical replicates. * $p<0.05$. Student's T test p values are shown for panel G and Kruskal-Wallis p values are shown for panel H.

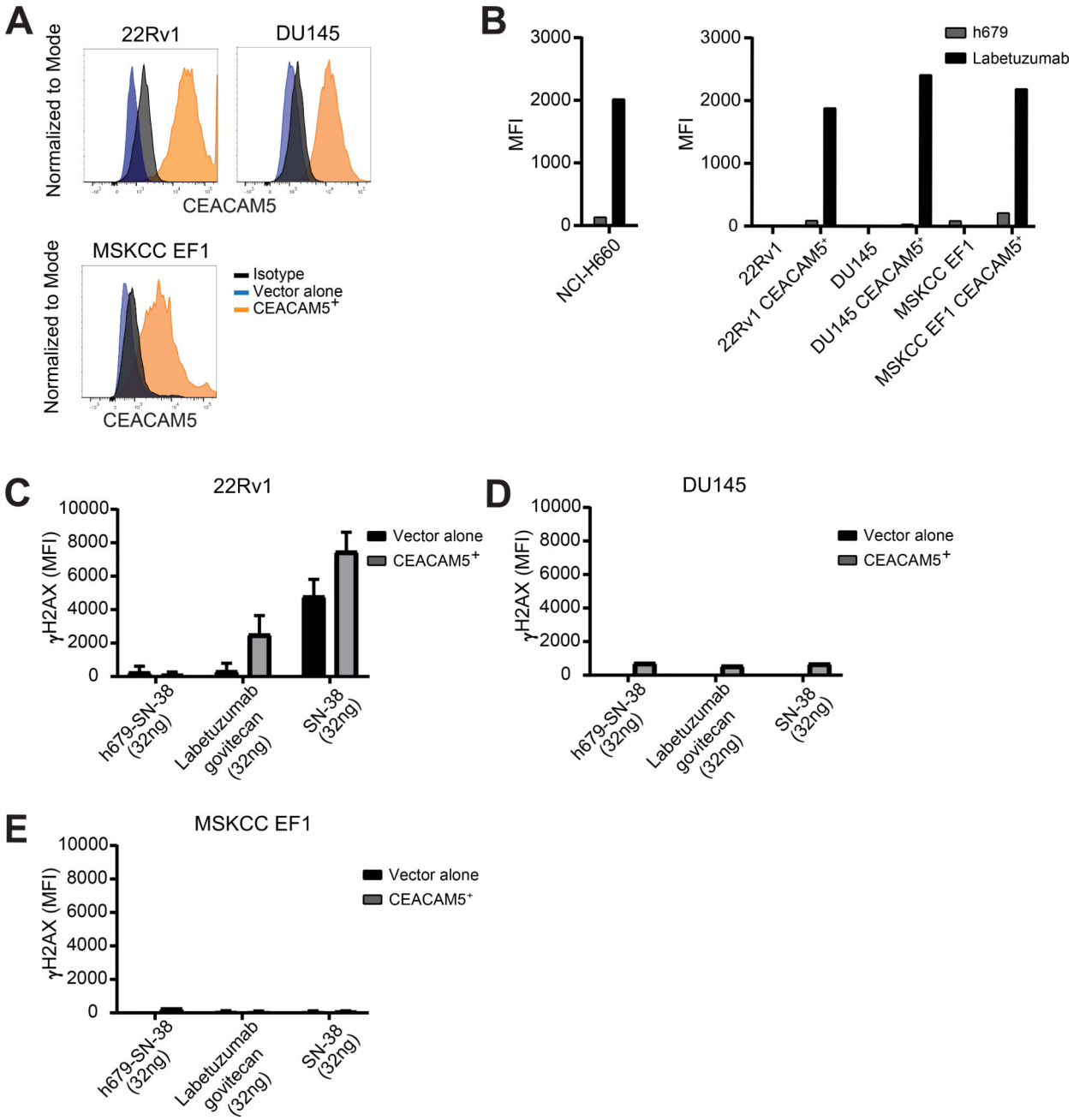


Figure 5. Labetuzumab govitecan induces dsDNA damage in a CEACAM5-specific manner.

(A) CEACAM5 surface protein expression determined by flow cytometry in prostate cancer cell lines transduced with lentiviral expression constructs. (B) Labetuzumab binding to CEACAM5 in prostate cancer cell lines. Measurement of intracellular γH2AX staining of (C) 22Rv1, (D) DU145, and (E) MSKCC EF1 cells 16 hours after treatment with h679-SN-38, labetuzumab govitecan, or SN-38 for 30 minutes on ice. MFI = Mean fluorescence intensity. Histograms depict means + SD for experimental duplicates.

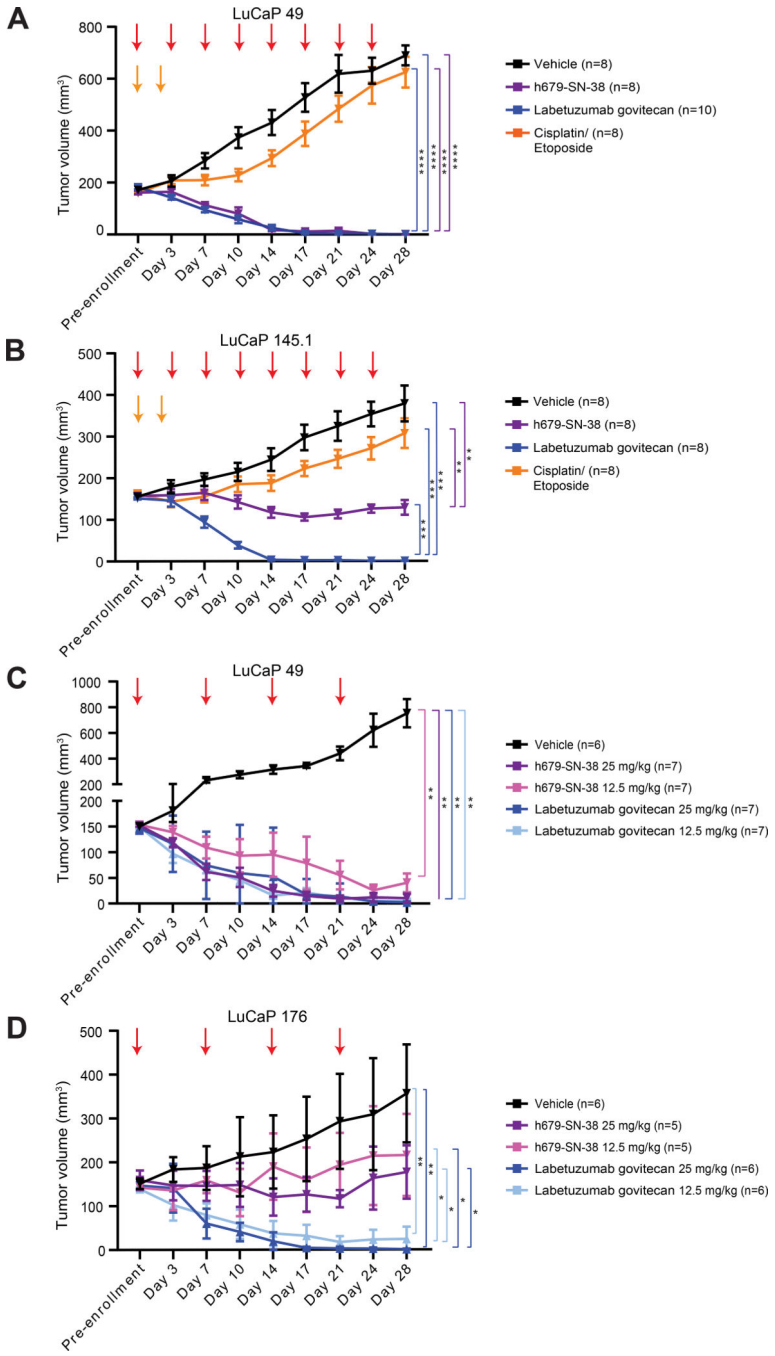


Figure 6. Labetuzumab govitecan eradicates CEACAM5^{+} LuCaP PDXs *in vivo*.

Tumor volumes monitored bi-weekly are shown for (A-B) single dose trials and (C-D) two dose trials. (A-B) Mice received eight treatments (red arrows) over 28 days with vehicle, h679-SN-38 (25 mg/kg), or labetuzumab govitecan (25 mg/kg). Cisplatin (5 mg/kg) was administered on day 0 and etoposide (8 mg/kg) was administered on days 0 and 2 (orange arrows). (C-D) Mice received four treatments (red arrows) over 28 days with vehicle, h679-SN-38, or labetuzumab govitecan at the doses indicated. Line graphs depict means ± SD. *

p<0.05; ** p<0.01; *** p<0.001; **** p<0.0001. Day 28 ANOVA p values are shown for all panels.

original reports

TRANSFORMER: A Randomized Phase II Study Comparing Bipolar Androgen Therapy Versus Enzalutamide in Asymptomatic Men With Castration-Resistant Metastatic Prostate Cancer

Samuel R. Denmeade, MD[1]; Hao Wang, PhD[1]; Neeraj Agarwal, MD[2]; David C. Smith, MD[3]; Michael T. Schweizer, MD[4]; Mark N. Stein, MD[5]; Vasileios Assikis, MD[6]; Przemyslaw W. Twardowski, MD[7]; Thomas W. Flaig, MD[8]; Russell Z. Szmulewitz, MD[9]; Jeffrey M. Holzbeierlein, MD[10]; Ralph J. Hauke, MD[11]; Guru Sonpavde, MD[12]; Jorge A. Garcia, MD[13]; Arif Hussain, MD[14]; Oliver Sartor, MD[15]; Shifeng Mao, MD[16]; Harry Cao, BS[1]; Wei Fu, PhD[1]; Ting Wang, BS[1]; Rehab Abdallah, MD[1]; Su Jin Lim, ScM[1]; Vanessa Bolejack, PhD[17]; Channing J. Paller, MD[1]; Michael A. Carducci, MD[1]; Mark C. Markowski, MD[1]; Mario A. Eisenberger, MD[1]; and Emmanuel S. Antonarakis, MD[1]; on behalf of the TRANSFORMER Investigators

abstract

PURPOSE Prostate cancer (PCa) becomes resistant to androgen ablation through adaptive upregulation of the androgen receptor in response to the low-testosterone microenvironment. Bipolar androgen therapy (BAT), defined as rapid cycling between high and low serum testosterone, disrupts this adaptive regulation in castration-resistant PCa (CRPC).

METHODS The TRANSFORMER (Testosterone Revival Abolishes Negative Symptoms, Fosters Objective Response and Modulates Enzalutamide Resistance) study is a randomized study comparing monthly BAT (n = 94) with enzalutamide (n = 101). The primary end point was clinical or radiographic progression-free survival (PFS); crossover was permitted at progression. Secondary end points included overall survival (OS), prostate-specific antigen (PSA) and objective response rates, PFS from randomization through crossover (PFS2), safety, and quality of life (QoL).

RESULTS The PFS was 5.7 months for both arms (hazard ratio [HR], 1.14; 95% CI, 0.83 to 1.55; $P = .42$). For BAT, 50% decline in PSA (PSA50) was 28.2% of patients versus 25.3% for enzalutamide. At crossover, PSA50 response occurred in 77.8% of patients crossing to enzalutamide and 23.4% to BAT. The PSA-PFS for enzalutamide increased from 3.8 months after abiraterone to 10.9 months after BAT. The PFS2 for BAT→enzalutamide was 28.2 versus 19.6 months for enzalutamide→BAT (HR, 0.44; 95% CI, 0.22 to 0.88; $P = .02$). OS was 32.9 months for BAT versus 29.0 months for enzalutamide (HR, 0.95; 95% CI, 0.66 to 1.39; $P = .80$). OS was 37.1 months for patients crossing from BAT to enzalutamide versus 30.2 months for the opposite sequence (HR, 0.68; 95% CI, 0.36 to 1.28; $P = .225$). BAT adverse events were primarily grade 1-2. Patient-reported QoL consistently favored BAT.

CONCLUSION This randomized trial establishes meaningful clinical activity and safety of BAT and supports additional study to determine its optimal clinical integration. BAT can sensitize CRPC to subsequent antiandrogen therapy. Further study is required to confirm whether sequential therapy with BAT and enzalutamide can improve survival in men with CRPC.

J Clin Oncol 39:1371-1382. © 2021 by American Society of Clinical Oncology

ASSOCIATED CONTENT

Data Supplement
Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on January 4, 2021 and published at ascopubs.org/journal/jco on February 22, 2021: DOI https://doi.org/10.1200/JCO.20.02759

INTRODUCTION

Since the discovery by Charles Huggins of remarkable palliative benefit from castration in men with symptomatic prostate cancer (PCa), the mainstay of treatment has been inhibition of androgen receptor (AR) function through primary androgen deprivation (ADT).[1] Although highly effective, therapeutic resistance is almost universal. Second-generation therapies that potently inhibit AR have become standard therapy based on modest improvements in survival versus placebo,[2,3] but resistance increases with each subsequent line of AR-directed therapy.[4-6] Importantly, PCa cells can develop resistance to androgen ablation through an adaptive marked upregulation of AR over time in response to low-androgen conditions (Data Supplement, online only).[7-9] Preclinical studies document that adaptive AR upregulation produces therapeutic vulnerability allowing PCa cells to be killed by exposure to supraphysiologic testosterone.[9-12] Episodic exposure to supraphysiologic testosterone can

CONTEXT

Key Objective

Is bipolar androgen therapy (BAT) superior to enzalutamide and does BAT overcome antiandrogen resistance in patients with metastatic prostate cancer progressing on abiraterone?

Knowledge Generated

BAT was not superior to enzalutamide but demonstrated similar time to progression and prostate-specific antigen response following treatment with abiraterone. BAT is safe, has meaningful clinical activity, can enhance quality of life, and markedly improve the magnitude and duration of response to enzalutamide.

Relevance

Sequential BAT→enzalutamide could be a safe and effective single third-line therapy for men with metastatic castration-resistant prostate cancer progressing on abiraterone. Further study is warranted to define the potential for this sequential treatment to produce significant survival improvement in men with castration-resistant prostate cancer.

produce downregulation of AR levels leading to potential resensitization to androgen-ablative therapies (Data Supplement).[13] Initial clinical studies documented the safety of rapid cycling between polar extremes of supraphysiologic and near-castrate serum testosterone, a concept termed bipolar androgen therapy (BAT), in asymptomatic men with metastatic castration-resistant PCa (CRPC).[14,15] The key findings have been that BAT was safe, did not accelerate disease progression, produced sustained prostate-specific antigen (PSA) and objective responses (ORs), and resensitized response to subsequent antiandrogens.[14,15]

Here, we hypothesized that BAT would have superior efficacy against PCa made resistant as a result of chronic exposure to low androgen and adaptively sensitize these cells to antiandrogens. We conducted the TRANSFORMER (Testosterone Revival Abolishes Negative Symptoms, Fosters Objective Response and Modulates Enzalutamide Resistance) trial to compare the effects of BAT versus the antiandrogen enzalutamide in asymptomatic men with CRPC progressing on abiraterone. Additionally, we explored the effect of sequential exposure to AR agonists or antagonists by allowing crossover to the opposite treatment upon progression.

METHODS

Trial Design

TRANSFORMER (ClinicalTrials.gov identifier: NCT02286921) was a multicenter, open-label, randomized, phase II trial whose objective was to determine the effectiveness of BAT versus enzalutamide on clinical or radiographic progression-free survival (PFS) in men with metastatic CRPC (mCRPC) progressing on abiraterone. Secondary objectives were to determine the effects on overall survival (OS), PSA-PFS, adverse events (AEs), and quality of life (QoL). Although crossover was not mandated, patients with radiographic progression on either arm who continued to meet eligibility requirements had the option to cross over to the opposite treatment. The objectives for this crossover were to evaluate time to PSA progression and time to second PSA progression from randomization through crossover treatment (termed PFS2). PSA50 response was an end point for both study phases.

Patients and Treatment

Eligible patients were asymptomatic with mCRPC documented by computed tomography (CT), technetium-99 bone scan, or both and Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of ≤ 2. Patients had evidence of PSA or radiographic progression after treatment with abiraterone acetate and prednisone. Patients were ineligible if they had pain because of mCRPC requiring treatment intervention or opioids or prior treatment with docetaxel or cabazitaxel for mCRPC. The Clinical Protocol and Data Supplement are available with the full text of this article (online only).

Patients were randomly assigned (1:1) to receive testosterone cypionate (at US Food and Drug Administration [FDA]–approved dose of 400 mg intramuscularly once every 28 days) or enzalutamide (160 mg by mouth daily) until clinical or radiographic progression or prohibitive toxicity. Patients were concurrently maintained on continuous testosterone suppression via surgical castration or luteinizing hormone–releasing hormone agonists or antagonists. At progression, asymptomatic patients who continued to meet eligibility requirements were allowed to cross over to alternate therapy. Clinical status and PSA were assessed each cycle during initial phase and crossover. CT and bone scan were obtained every 12 weeks during initial phase but not at crossover. Patients on either study arm with clinical progression because of pain from PCa were not permitted to cross over. QoL was assessed at baseline and 1, 3, 6, and 12 months postrandomization using RAND-SF36 Quality of Life Survey, FACIT-F Version 4, I-PANAS-SF, International Index of Erectile Function (IIEF), and the Brief Pain Inventory, respectively.

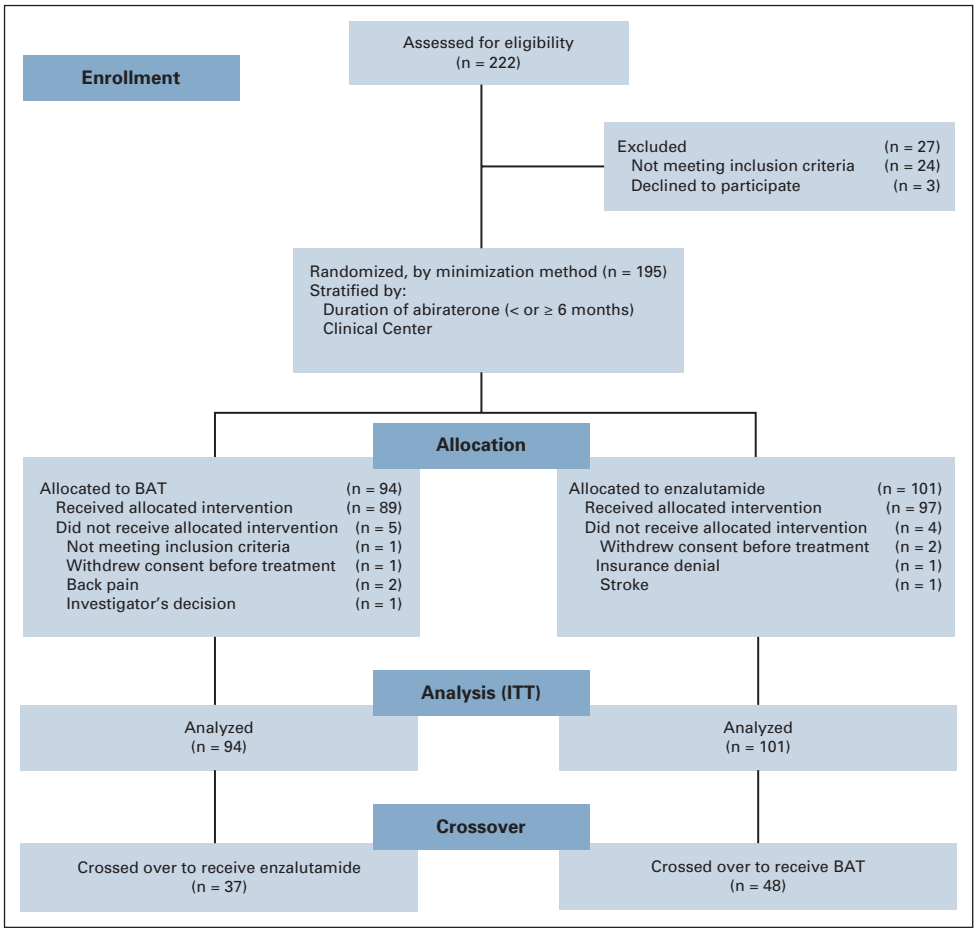


FIG 1. TRANSFORMER CONSORT diagram. BAT, bipolar androgen therapy.

Randomization was performed centrally using a minimization approach, with stratification by length of prior abiraterone exposure (< or ≥ 6 months) and clinical center.

Trial Oversight

The trial was designed and led by the principal investigator (S.R.D.) and co-investigators at Johns Hopkins (M.A.E. and E.S.A.). The trial was conducted at 17 US academic centers. The authors were solely responsible for writing the manuscript.

A Transformative Impact Award from the Department of Defense (DoD) provided financial support for trial conduct. DoD representatives reviewed and approved the protocol and consent documents at each participating site but were not otherwise involved in any study aspect. ADT, enzalutamide, testosterone cypionate, and all subsequent treatments were accessed and administered according to local standard practice. The authors vouch for the accuracy and completeness of the reported data and for fidelity to the protocol.

An independent data and safety monitoring committee reviewed the progress and results of the trial. The trial was conducted in accordance with the principles of Good Clinical Practice guidelines and Declaration of Helsinki. The protocol was independently reviewed and approved as required at each participating institution. All patients provided written informed consent.

End Points

The primary end point of clinical or radiographic PFS was measured as the interval from randomization to the earliest sign of radiographic progression according to the criteria of the PCa Working Group 2 (PCWG2) for bone lesions and the RECIST version 1.1 for soft-tissue lesions, the development of symptoms or complications attributable to cancer progression, or the initiation of another anticancer treatment for PCa[16] and censored at the date of last scan or clinical visit for those who did not have the event at the time of data cutoff. The secondary end point of OS was the interval from randomization to death and censored at the date of last known alive. PSA-PFS was measured as the interval from randomization to the time of PSA progression according to the PCWG2 criteria (a confirmed relative increase in the PSA level from the nadir value by ≥ 25% and by ≥ 2 ng/mL) or censored at the last date of PSA assessment for patients without PSA progression. The secondary end point PFS2 was defined as the interval from randomization to second

TABLE 1. Characteristics of the Patients at Baseline

Characteristic	BAT (n = 94)	Enzalutamide (n = 101)
Median age (range), years	71.0 (45.0-87.0)	71.0 (49.0-91.0)
Race, n (%)		
American Indian	1 (1.1)	0
Asian	2 (2.1)	3 (3.0)
Black or African American	7 (7.4)	7 (6.9)
White	82 (87.2)	88 (87.1)
Other	2 (2.1)	3 (3.0)
Ethnic group, n (%)		
Hispanic or Latino	4 (4.3)	2 (2.0)
Not Hispanic or Latino	86 (91.5)	97 (96.0)
Unknown	4 (4.3)	2 (2.0)
ECOG PS, n (%)		
0	53 (56.4)	73 (72.3)
1	40 (42.6)	25 (24.8)
2	1 (1.1)	1 (1.0)
Missing	0	2 (2.0)
Gleason sum, n (%)		
≤ 5	4 (4.3)	1 (1)
6	4 (4.3)	13 (12.9)
7	22 (23.4)	27 (26.7)
8	21 (22.3)	10 (9.9)
9-10	39 (41.5)	44 (43.6)
Missing	4 (4.3)	6 (5.9)
Baseline PSA, mean (range)	44.3 (1.1-323.3)	50.6 (1.1-559.2)
Baseline alkaline phosphatase, mean (range)	113.3 (41-992)	94.1 (34-284)
Duration of prior abiraterone, months (%)		
≤ 6 months	18 (19.1)	19 (18.8)
> 6 months	76 (80.9)	82 (81.2)
Prior therapy type, n (%)		
Radiation (primary)	50 (53.2)	48 (47.5)
Surgery (prostatectomy)	40 (42.6)	47 (46.5)
Secondary hormonal therapy	91 (96.8)	97 (96.0)
Docetaxel chemotherapy	13 (13.8)	11 (10.9)
Investigational	21 (22.3)	20 (19.8)
Total number of metastases, median (range)	2 (1-10)	2 (1-8)
Patients with visceral metastases, n (%)	52 (55.3)	62 (61.4)

Abbreviations: BAT, bipolar androgen therapy; ECOG, Eastern Cooperative Oncology Group; PS, performance status; PSA, prostate-specific antigen.

PSA progression following crossover therapy. For patients who did not cross over, PFS2 was censored at the time of PFS or last follow-up with no progression on initial treatment. OR was defined as complete response or partial response per RECIST and PCWG2 among those with measurable baseline disease. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.02. AE data were collected during the treatment period, with a final safety assessment performed 30-42 days after the cessation of the trial regimen.

Statistical Analysis

Assuming a median PFS of 6 months in the enzalutamide group on the basis of two previous studies of enzalutamide in patients with mCRPC progressing on abiraterone, we determined that enrollment of 194 patients (with 156 PFS

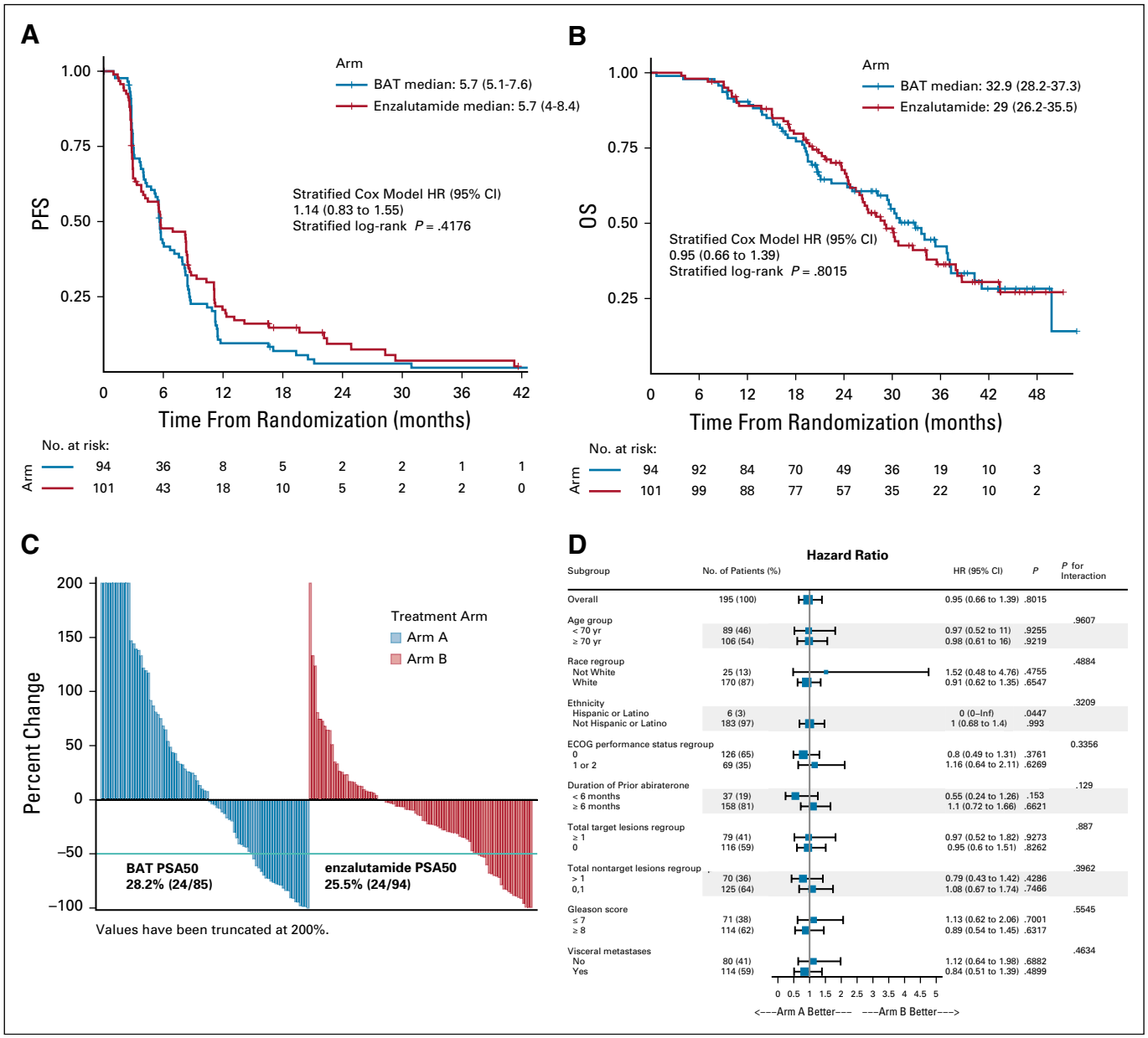


FIG 2. Kaplan-Meier estimates of (A) PFS and (B) OS, (C) waterfall plot of PSA response to initial therapy, (D) subgroup analysis of OS. BAT, bipolar androgen therapy; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; INF, infinity; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen.

events) would provide a power of 80% to detect a hazard ratio (HR) of 0.667 in the BAT group versus the enzalutamide group, with a one-sided type I error of 0.05. Two interim analyses of efficacy and futility for PFS were conducted as planned, the first after approximately 45% of the information and the second after 70% of the information. An independent data and safety monitoring committee reviewed interim data and recommended to continue to full accrual.

The primary efficacy end point PFS and the secondary efficacy end points PSA-PFS, OS, and PFS2 were based on the intention-to-treat principle and included all patients who had undergone randomization. Patients who had undergone randomization and received a dose of any trial drug were included in safety analyses.

PFS and other time-to-event end points were estimated using Kaplan-Meier method, and each was compared between the arms using a stratified log-rank test, with stratification factor of duration of prior abiraterone treatment (< or ≥ 6 months). The Cox regression model, stratified for the same baseline stratification factor, was used to estimate HRs between the two arms and

TABLE 2. Prespecified Secondary Efficacy End Points (ITT Population)

End Point	n	BAT	95% CI	n	Enzalutamide	95% CI	HR	P
Initial treatment								
Time to PSA progression, months	91	2.79	1.81 to 4.50	98	3.81	2.8 to 6.4	1.53 (1.08-2.19)	.0181
Unverified PSA50 response, n (%)	85	24 (28.2)		94	24 (25.5)			.7908
OR, n (%)	33	8 (24.2)		24	1 (4.2)			.072
Radiographic PFS, months	94	6.05	5.56 to 8.42	101	8.29	5.69 to 11.09	1.24 (0.87-1.77)	.2332
OS, months	94	32.9	28.2 to 37.3	101	29	26.2 to 35.5	0.95 (0.66-1.39)	.8015
OS, all patients	195	30.1	27 to 34.3					
Duration of abiraterone treatment								
< 6 months, %	18	19.1		19	18.8		0.60 (0.29-1.25)	.1742
≥ 6 months, %	76	80.9		82	81.2		1.31 (0.93-1.84)	.1252
Crossover treatment		**BAT to enzalutamide**			**Enzalutamide to BAT**			
Time to PSA progression, months	36	10.9	6.1 to NA	47	1.1	0.9 to 7.6		.0001
Unverified PSA50 response, n (%)	36	28 (77.8)		47	10 (21.3)			
OR, n (%)	35	10 (28.6)	0.15 to 0.46	41	3 (7.3)	0.02 to 0.20		.03
PFS2, months	94	28.2	23.6 to NA	101	19.6	12.9 to 29.7	0.44 (0.22-0.88)	.0152
OS (BAT-enzalutamide *v* enzalutamide-BAT), months	37	37.1	30.5 to NA	46	30.2	25.9 to NA	0.68 (0.36-1.28)	.2252
OS (BAT-enzalutamide *v* enzalutamide only), months	37	37.1	30.5 to NA	53	28.6	24.3 to 35.5	0.52 (0.29-0.96)	.031
OS (BAT-enzalutamide *v* BAT only), months	37	37.1	30.5 to NA	57	25	20 to 34	0.46 (0.25-0.84)	.0092

Abbreviations: BAT, bipolar androgen therapy; HR, hazard ratio; ITT, intention-to-treat; NA, not available; OR, objective response; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen.

corresponding 95% CIs. For each QoL module, summary statistics of scores was reported at baseline and 1, 3, 6, and 12 months postrandomization. Scores at each follow-up time, as well as change pre- and post-treatment, were compared between the arms using Mann-Whitney tests.

RESULTS

From April 2015 to April 2018, we randomly assigned 195 men to receive either BAT (94 patients) or enzalutamide (101 patients) across 17 sites in the United States (Fig 1). The data cutoff date for this report was November 2019; median follow-up time among patients who are alive is 31.9 months. Baseline characteristics of all the patients are summarized in Table 1.

Primary End Point

The primary analysis of PFS was performed in November 2018, after progression had occurred in 156 patients. The median PFS was 5.6 months in the BAT arm versus 5.7 months in the enzalutamide arm (HR, 1.13; 95% CI, 0.82 to 1.57; $P = .45$) (Fig 2A). With additional follow-up at data cutoff in November 2019, results remained unchanged (5.7 months for both arms; HR, 1.14; 95% CI, 0.83 to 1.55; $P = .42$). In a prespecified analysis, PFS in men with short prior response to abiraterone (< 6 months) favored BAT (HR, 0.60; 95% CI, 0.29 to 1.25), whereas PFS in those with longer prior response to abiraterone (≥ 6 months) favored enzalutamide (HR, 1.31; 95% CI, 0.93 to 1.84; $P_{interaction} = .10$) (Table 2 and Data Supplement).

Secondary End Points

Median OS was not statistically different, but hypothesis-generating, for the BAT arm compared with the enzalutamide arm (32.9 *v* 29.0 months; HR, 0.95; 95% CI, 0.66 to 1.39; $P = .80$) (Fig 2B and Table 2). In a subset analysis, OS in men with short prior response to abiraterone (< 6 months) favored BAT (HR, 0.55; 95% CI, 0.24 to 1.26), whereas OS in those with longer prior response to abiraterone (≥ 6 months) favored enzalutamide (HR, 1.08; 95% CI, 0.71 to 1.64; $P_{interaction} = .14$) (Fig 2D). The percentage of patients who achieved a PSA50 response during the initial phase of treatment was similar between the two groups (28.2% [24/85] for BAT versus 25.5% [24/94] for enzalutamide) (Fig 2C and Table 2). Time to first PSA progression was short for both the groups but favored the enzalutamide arm (2.8 months for BAT *v* 3.8 months for enzalutamide; HR, 1.51; 95% CI, 1.06 to 2.16; $P = .02$) (Table 2). Conversely, the OR rate favored the BAT group over enzalutamide (24.2% [8/33] *v* 4.2% [1/24], respectively; $P = .07$) (Table 2).

Crossover Treatment

Patients who remained asymptomatic and continued to meet eligibility requirements were provided the opportunity

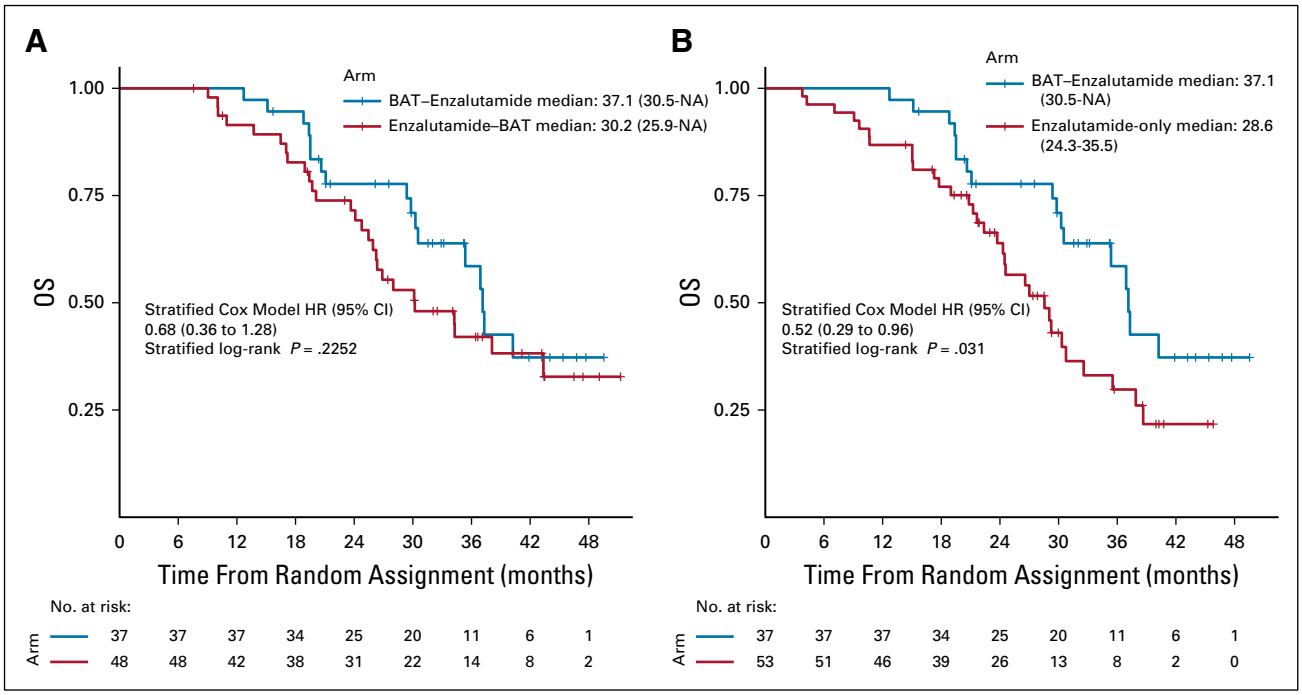


FIG 3. Kaplan-Meier estimates of OS in the crossover population. (A) Comparison of OS in the subset of patients receiving BAT→enzalutamide versus enzalutamide→BAT, after eliminating those who came off study without crossing over. (B) Comparison of OS in the subset of patients receiving BAT→enzalutamide (after eliminating patients who did not cross over) versus enzalutamide-only patients who did not cross over to receive BAT. BAT, bipolar androgen therapy; HR, hazard ratio; NA, not accessible; OS, overall survival.

to cross over, after a 28-day washout period, to the alternate treatment at time of progression. Crossover was not permitted in patients in either arm with clinical progression because of pain from PCa. Overall, 37 (39.3%) patients initially on BAT crossed over to receive enzalutamide, whereas 48 (47.6%) patients crossed from enzalutamide to BAT (Table 1). For patients who did not cross over, approximately equal numbers (14% on BAT and 18% on enzalutamide) had clinical progression. Overall, 37% of patients receiving BAT and 43% receiving enzalutamide crossed over as a result of radiographic progression (Data Supplement).

The majority of the patients who crossed over did so as a result of radiographic progression (95% of the BAT group and 90% of the enzalutamide group) (Data Supplement). There was no significant difference in characteristics (age, ECOG PS, race, ethnicity, target lesions, nontarget lesions, and duration of prior abiraterone therapy) of the crossover population compared with the noncrossover population (Data Supplement). Characteristics of each crossover arm were similar (Data Supplement). Crossover to enzalutamide following BAT was associated with greater benefits than crossover to BAT following enzalutamide, for all secondary end points (Table 2). Median OS for those crossing over to enzalutamide post-BAT was 37.1 months versus 30.2 months for those crossing to BAT postenzalutamide (HR, 0.68; 95% CI, 0.36 to 1.28; $P = .23$) (Fig 3A and Table 1) versus 28.6 months for those who received enzalutamide-only without crossover (HR, 0.52; 95% CI, 0.29 to 0.96; $P = .03$) versus 25 months (HR, 0.46; 95% CI, 0.25 to 0.84; $P = .009$) for those who received BAT-only without crossover (Fig 3B and Table 1). The OR of 28.6% (10/35) for enzalutamide post-BAT was higher than the response of 7.3% (3/41) with BAT postenzalutamide (Table 2). The PSA50 response was 77.8% (28/36) for those who crossed to enzalutamide compared with 21.3% (10/47) for those who crossed to BAT (Fig 4A and Table 1). Patients receiving enzalutamide immediately after abiraterone had significantly shorter median PSA-PFS with enzalutamide (3.8 months) compared with those who received enzalutamide following BAT (10.9 months) (HR, 0.45; 95% CI, 0.24 to 0.86; $P = .008$) (Table 2).

Considering the sequencing of BAT and enzalutamide, patients who received the treatment sequence of BAT→enzalutamide had significantly longer PFS2 compared with the opposite sequence (28.2 *v* 19.6 months; HR, 0.44; 95% CI, 0.22 to 0.88; $P = .02$) (Fig 4B and Data Supplement). Subgroup analysis of PFS2 favored the BAT→enzalutamide sequence (arm A) across all subgroups (Fig 4C).

Androgen Receptor Expression

Baseline blood samples (n = 187) were analyzed for transcript expression of full-length AR (AR-FL) and the truncated ligand-independent AR variant (AR-V7) in circulating tumor cells (CTCs), according to previously published methods.[17] Overall, 41% of patients on BAT and 37%

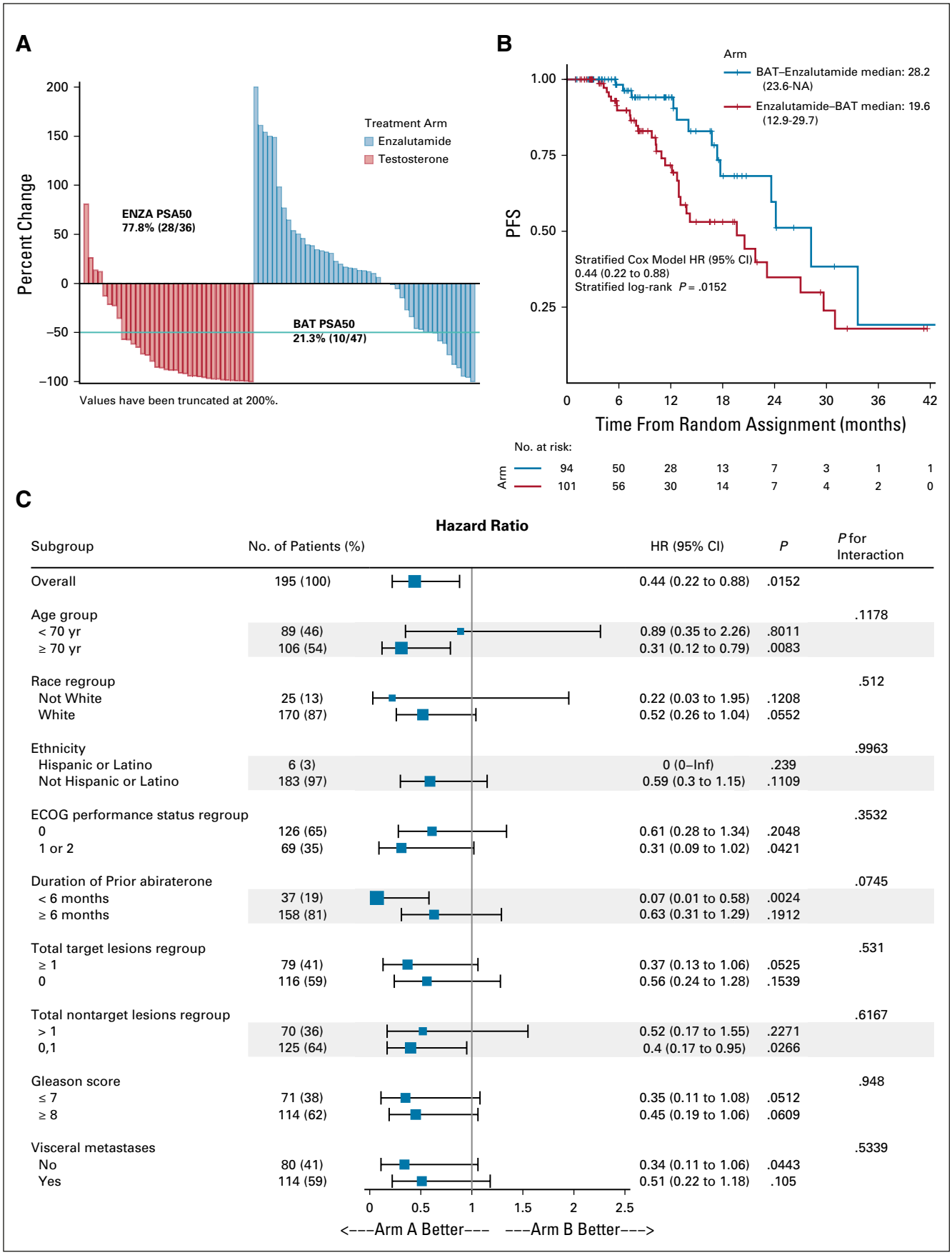


FIG 4. (A) Waterfall plot of PSA response to crossover therapy, (B) Kaplan-Meier estimates of PFS2, (C) subgroup analysis of PFS2. BAT, bipolar androgen therapy; ECOG, Eastern Cooperative Oncology Group; PFS, progression-free survival; PSA, prostate-specific antigen.

TABLE 3. Effect of AR-FL and AR-V7 Expression on PFS and OS

	BAT				Enzalutamide			
AR Isotype	**Positive**	**Negative**	**HR**	***P***	**Positive**	**Negative**	**HR**	***P***
AR-FL								
n (%)	37 (41.1)	53 (58.9)			36 (37.1)	61 (62.9)		
PFS, months	4.6	5.8	1.70 (1.05-2.76)	.0321	3	8.3	1.99 (1.25-3.15)	.0044
OS, months	29.6	32.9	1.48 (0.82-2.68)	.1909	28	30.3	1.55 (0.9-2.66)	.1225
AR-V7								
n (%)	11 (12.2)	79 (87.8)			7 (7.2)	90 (92.8)		
PFS, months	4	5.8	2.07 (1.0-4.16)	.0719	2.5	5.7	3.0 (1.30-6.93)	.022
OS, months	13.8	34	6.08 (2.95-12.54)	< .001	17.3	30.2	3.08 (1.17-8.15)	.0451

Abbreviations: AR, androgen receptor; BAT, bipolar androgen therapy; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

on enzalutamide tested positive for AR-FL, consistent with increased AR expression in CTCs following abiraterone pretreatment (Table 3). AR-V7 transcript was detected at baseline in 12% of patients on BAT and 7% on enzalutamide (Table 3). Detection of AR-FL and AR-V7 transcripts were both generally associated with shorter PFS and OS on BAT and enzalutamide (although not all differences were statistically significant), consistent with the broad negative prognostic impact in patients with mCRPC (Table 3 and Data Supplement).[17] However, neither AR-FL nor AR-V7 status was predictive of better or worse clinical outcomes using BAT or enzalutamide, suggesting that neither factor can be used as a treatment selection biomarker in this context.

Safety and QoL

The majority of AEs were grade 1-2 (BAT, 68.5%; enzalutamide, 62.8%); grade 3-4 AEs occurred in 28.1% of patients on BAT and 35.1% on enzalutamide (Table 4). Only one grade 5 AE of death not otherwise specified was observed in a patient on enzalutamide. Serious AEs occurred in 19.1% of patients on BAT and 20.6% on enzalutamide. The percentage discontinuing therapy as a result of AEs was slightly higher for BAT (9.0%) than enzalutamide (5.2%) (Table 4).

The incidence of AEs was generally similar in the two groups. Notable exceptions included fatigue with 48.5% of patients on enzalutamide experiencing grade 1-2 and 7.2% of patients grade 3-4 fatigue, compared with 31.5% of BAT patients experiencing only grade 1-2 fatigue. Enzalutamide was associated with a higher percentage of constitutional symptoms such as anorexia, depression, anxiety, insomnia, headache, and generalized muscle weakness as well as GI complaints (diarrhea, constipation, abdominal pain, and flatulence). BAT was associated with increased sexual side effects (hot flashes, breast tenderness, and gynecomastia) and musculoskeletal complaints (peripheral edema and generalized musculoskeletal pain).

Patient-reported QoL consistently favored BAT at 1, 3, and 6 months after initiation of treatment (Data Supplement).

DISCUSSION

The TRANSFORMER trial is unique in that it compares two treatments with diametrically opposite effects on the AR therapeutic target. In this trial, BAT was not superior to enzalutamide with respect to the primary end point clinical or radiographic PFS in asymptomatic men with mCRPC progressing on abiraterone. Although not powered to show equivalency, the treatments were similar in terms of median PFS (5.7 months in both the arms), time to PSA progression (2.8 *v* 3.8 months), and PSA50 responses (28.2% *v* 25.5%). The similarity of response, despite the opposing nature of the treatments, may relate to PCa cells' ability to adaptively regulate AR levels in response to androgen levels. Interestingly, the greatest benefit from BAT was in patients experiencing progression on prior abiraterone within 6 months, suggesting that BAT may partially reverse lineage plasticity in PCa cells losing AR addiction.[18] Unfortunately, neither baseline AR-FL nor AR-V7 expression was identified as a potential treatment selection biomarker. However, consistent with the hypothesis that increased AR-FL can make PCa resistant to androgen ablation but vulnerable to high-dose testosterone,[9] PFS was significantly increased for BAT and decreased for enzalutamide in AR-FL–positive patients (Table 3).

BAT also maintained or improved QoL, particularly in domains of fatigue and physical and sexual function compared with enzalutamide. The incidence of AEs was similar between treatments and primarily low-grade. BAT was associated with less fatigue and GI and constitutional symptoms but increased edema, generalized pain, and sexual side effects compared with enzalutamide.

Approximately 40% of patients crossed over to the opposite treatment at progression. There were no significant differences between noncrossover versus crossover patient characteristics. Patients who crossed to enzalutamide post-BAT showed significantly enhanced response compared with those who received enzalutamide immediately after progression on abiraterone. Median time to PSA progression increased to 10.9 months compared with 3.8 months,

TABLE 4. Summary of AEs During Initial Treatment (Safety Analysis Population)

	BAT (n = 89)		Enzalutamide (n = 97)	
AE	**Any Grade, n (%)**	**Grade 3 or 4, n (%)**	**Any Grade, n (%)**	**Grade 3 or 4, n (%)**
Any AE	86 (96.6)	25 (28.1)	95 (97.9)	34 (35.1)
Serious AE	17 (19.1)		20 (20.6)	
Grade 5 AE	0		1 (1.0)	
AE leading to discontinuation of the trial	8 (9.0)		5 (5.2)	
AE that occurred in ≥ 5% of patients in either group	Grade 1 or 2, n (%)	Grade 3 or 4, n (%)	Grade 1 or 2, n (%)	Grade 3 or 4, n (%)
Fatigue	28 (31.5)	0	47 (48.5)	7 (7.2)
Generalized pain	28 (31.5)	3 (3.4)	16 (16.5)	1 (1.0)
Edema limbs	21 (23.6)	1 (1.1)	11 (11.3)	0
Localized edema	8 (9.0)		6 (6.2)	
Back pain	18 (20.2)	3 (3.4)	12 (12.4)	7 (7.2)
Pain in extremity	13 (14.6)	1 (1.1)	14 (14.4)	2 (2.1)
Bone pain	10 (11.2)	0	6 (6.2)	1 (1.0)
Arthralgia	4 (4.5)	1 (1.1)	9 (9.3)	0
Myalgia	4 (4.5)	0	7 (7.2)	1 (1.0)
Generalized muscle weakness	2 (2.2)		7 (7.2)	
Diarrhea	10 (11.2)		23 (23.7)	
Nausea	12 (13.5)	1 (1.0)	21 (21.6)	1 (1.0)
Constipation	14 (15.7)		13 (13.4)	
Vomiting	4 (4.5)		7 (7.2)	
Abdominal pain	1 (1.1)		5 (5.2)	
Flatulence	1 (1.1)		6 (6.2)	
GERD	0		5 (5.2)	
Anorexia	11 (12.4)	0	27 (27.8)	2 (2.1)
Hypertriglyceridemia	5 (5.6)	0	5 (5.2)	1 (1.0)
Hyperglycemia	2 (2.2)		5 (5.2)	
Headache	5 (5.6)		14 (14.4)	
Dizziness	7 (7.9)		9 (9.3)	
Paresthesia	3 (3.4)		7 (7.2)	
Weight loss	6 (6.7)		13 (13.4)	
Alkaline phosphatase increased	3 (3.4)		9 (9.3)	
Creatinine increased	8 (9.0)		4 (4.1)	
Insomnia	5 (5.6)	0	13 (13.4)	1 (1.0)
Depression	1 (1.1)		13 (13.4)	
Anxiety	2 (2.2)		9 (9.3)	
Cough	12 (13.5)		11 (11.3)	
Dyspnea	9 (10.1)			
AEs of interest				
Hematuria	6 (6.7)	1 (1.1)	6 (6.2)	0
Urinary frequency	6 (6.7)		4 (4.1)	
Urinary retention	2 (2.2)		5 (5.2)	
Urinary urgency	3 (3.4)		1 (1.0)	
Hemoglobin increased	3 (3.4)		0	

(continued on following page)

TABLE 4. Summary of AEs During Initial Treatment (Safety Analysis Population) (continued)

	BAT (n = 89)		Enzalutamide (n = 97)	
AE	**Any Grade, n (%)**	**Grade 3 or 4, n (%)**	**Any Grade, n (%)**	**Grade 3 or 4, n (%)**
Mood swings	1 (1.1)		0	
Increased temper or anger	1 (1.1)		0	
Personality change	1 (1.1)		0	
Hypertension	2 (2.2)	0	3 (3.1)	4 (4.1)
Seizures	0		0	
Stroke	1 (1.1)		0	
Thrombolic event	1 (1.1)	0	0	2 (2.1)
Chest pain	1 (1.1)		1 (1.0)	
Palpitations	1 (1.1)		1 (1.0)	
Testicular pain	4 (4.5)		1 (1.0)	
Breast pain or tenderness	5 (5.6)		0	
Gynecomastia	4 (4.5)		0	
Hot flashes	7 (7.9)		10 (10.3)	

Abbreviations: AE, adverse event; BAT, bipolar androgen therapy; GERD, gastroesophageal reflux disease.

PSA50 response improved to 78% versus 25%, and OR improved to 29% versus 4%. Overall, our results support our hypothesis that BAT may reverse antiandrogen resistance via adaptive downregulation of AR expression (Data Supplement).

The use of PSA progression is nuanced because PSA expression is directly stimulated by testosterone, which could likely shorten time to PSA progression on BAT. However, as an exploratory end point we measured PFS2, which was significantly increased for patients treated with BAT→enzalutamide compared with the opposite sequence (28.2 *v* 19.6 months, respectively). Although our PFS2 results do not include the duration of treatment with prior abiraterone, they compare favorably with Khalaf et al[19] who reported median PFS2 of 19.3 months in 73 patients treated with abiraterone followed by enzalutamide. Median survival of 25-28 months has been reported in small studies of patients with mCRPC receiving abiraterone followed by enzalutamide.[19-21] In contrast, in our study, median postabiraterone survival for BAT→enzalutamide was 37.1 months.

In conclusion, TRANSFORMER establishes meaningful clinical activity of BAT and supports additional study to determine its optimal clinical integration. Although the trial failed to demonstrate superior PFS with BAT over enzalutamide in postabiraterone CRPC, it demonstrated that BAT is safe, enhances QoL, and has efficacy comparable to enzalutamide in this patient population. However, the most important finding is that postabiraterone, BAT can markedly improve the magnitude and duration of response to enzalutamide when used as an intervening therapy. These results support further evaluation of sequential BAT→enzalutamide as a single therapy. Further study is warranted to define the potential for sequential treatment to produce significant survival improvement in men with CRPC.

AFFILIATIONS

[1]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD
[2]The Huntsman Cancer Institute, Salt Lake City, UT
[3]The University of Michigan, Ann Arbor, MI
[4]The University of Washington, Seattle, WA
[5]Rutgers University, New Brunswick, NJ
[6]Piedmont Cancer Institute, Atlanta, GA
[7]City of Hope Cancer Center, Duarte, CA
[8]University of Colorado, Aurora, CO
[9]University of Chicago, Chicago, IL
[10]University of Kansas, Kansas City, KA
[11]Nebraska Cancer Specialists, Omaha, NE
[12]University of Alabama at Birmingham, Birmingham, AL
[13]The Cleveland Clinic, Cleveland, OH
[14]The University of Maryland, Baltimore, MD
[15]Tulane University, New Orleans, LA
[16]Allegheny General Hospital, Pittsburgh, PA
[17]Cancer Research and Biostatistics, Seattle, WA

CORRESPONDING AUTHOR

Samuel R. Denmeade, MD, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Viragh Cancer Building 9-121, 201 N. Broadway, Baltimore, MD 21287; e-mail: denmesa@jhmi.edu.

SUPPORT

Supported by a Transformative Grant (W81XWH-14-2-0189) from the Department of Defense PCa Research Program.

CLINICAL TRIAL INFORMATION

ClinicalTrials.gov identifier: NCT02286921

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.20.02759.

AUTHOR CONTRIBUTIONS

Conception and design: Samuel R. Denmeade, Hao Wang, Przemyslaw W. Twardowski, Michael A. Carducci, Mario A. Eisenberger, Emmanuel S. Antonarakis
Administrative support: Neeraj Agarwal, Guru Sonpavde, Harry Cao, Ting Wang, Rehab Abdallah
Provision of study materials or patients: Neeraj Agarwal, David C. Smith, Vasileios Assikis, Russell Z. Szmulewitz, Ralph J. Hauke, Guru Sonpavde, Jorge A. Garcia, Oliver Sartor, Michael A. Carducci, Mark C. Markowski, Emmanuel S. Antonarakis
Collection and assembly of data: Samuel R. Denmeade, Neeraj Agarwal, David C. Smith, Michael T. Schweizer, Mark N. Stein, Vasileios Assikis, Russell Z. Szmulewitz, Jeffrey M. Holzbeierlein, Ralph J. Hauke, Guru Sonpavde, Arif Hussain, Oliver Sartor, Shifeng Mao, Harry Cao, Ting Wang, Rehab Abdallah, Vanessa Bolejack, Michael A. Carducci, Mark C. Markowski
Data analysis and interpretation: Samuel R. Denmeade, Hao Wang, Neeraj Agarwal, David C. Smith, Michael T. Schweizer, Mark N. Stein, Vasileios Assikis, Thomas W. Flaig, Russell Z. Szmulewitz, Ralph J. Hauke, Jorge A. Garcia, Arif Hussain, Oliver Sartor, Wei Fu, Su Jin Lim, Vanessa Bolejack, Channing J. Paller, Michael A. Carducci, Mark C. Markowski, Mario A. Eisenberger, Emmanuel S. Antonarakis
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

We thank the many patients who participated in this trial; the nurses, study coordinators, and research administrators at the participating hospitals; the administrative support of Nrushinga Mishra, Joshua McKean, and Melissa Cunningham at the DoD PCRP; and the members of the independent data monitoring committee: Dr Charles Ryan, Dr George Wilding, and Dr Christine Hann. In memory of Mr Bruce Hunsicker, founder of the One-in-Six Foundation, Akron, OH.

REFERENCES

1. Huggins C, Hodges CV: Studies on prostatic cancer. I. The effect of castration, of estrogen and androgen injection on serum phosphatases in metastatic carcinoma of the prostate. Cancer Res 1:293-297, 1941
2. Beer TM, Armstrong AJ, Rathkopf DE, et al: Enzalutamide in metastatic PCa before chemotherapy. N Engl J Med 371:424-433, 2014
3. Ryan CJ, Smith MR, de Bono JS, et al: Abiraterone in metastatic PCa without previous chemotherapy. N Engl J Med 368:138-148, 2013
4. Emamekhoo H, Barata PC, Edwin NC, et al: Evaluation of response to enzalutamide consecutively after abiraterone acetate/prednisone failure in patients with metastatic castration-resistant PCa. Clin Genitourin Cancer 16:429-436, 2018
5. Smith MR, Saad F, Rathkopf DE, et al: Clinical outcomes from androgen signaling-directed therapy after treatment with abiraterone acetate and prednisone in patients with metastatic castration-resistant PCa: Post hoc analysis of COU-AA-302. Eur Urol 72:10-13, 2017
6. de Bono JS, Chowdhury S, Feyerabend S, et al: Antitumour activity and safety of enzalutamide in patients with metastatic castration-resistant PCa previously treated with abiraterone acetate plus prednisone for >24 weeks in Europe. Eur Urol 74:37-45, 2018
7. Linja MJ, Savinainen KJ, Saramaki OR, et al: Amplification and overexpression of androgen receptor gene in hormone-refractory PCa. Cancer Res 61: 3550-3555, 2001
8. Chen CD, Welsbie DS, Tran C, et al: Molecular determinants of resistance to antiandrogen therapy. Nat Med 10:33-39, 2004
9. Isaacs JT, D'Antonio JM, Chen S, et al: Adaptive auto-regulation of androgen receptor provides a paradigm shifting rationale for bipolar androgen therapy (BAT) for castrate resistant human PCa. Prostate 72:1491-1505, 2012
10. Umekita Y, Hiipakka RA, Kokontis JM, et al: Human prostate tumor growth in athymic mice: Inhibition by androgens and stimulation by finasteride. Proc Natl Acad Sci U S A 93:11802-11807, 1996
11. Litvinov IV, Vander Griend DJ, Antony L, et al: Androgen receptor as a licensing factor for DNA replication in androgen-sensitive PCa cells. Proc Natl Acad Sci U S A 103:15085-15090, 2006
12. Vander Griend DJ, Litvinov IV, Isaacs JT: Stabilizing androgen receptor in mitosis inhibits PCa proliferation. Cell Cycle 6:647-651, 2007
13. Denmeade SR, Isaacs JT: Bipolar androgen therapy: The rationale for rapid cycling of supraphysiologic androgen/ablation in men with castration resistant PCa. Prostate 70:1600-1607, 2010
14. Schweizer MT, Antonarakis ES, Wang H, et al: Effect of bipolar androgen therapy for asymptomatic men with castration-resistant PCa: Results from a pilot clinical study. Sci Transl Med 7:269ra2, 2015
15. Teply BA, Wang H, Luber B, et al: Bipolar androgen therapy in men with metastatic castration-resistant PCa after progression on enzalutamide: An open-label, phase 2, multicohort study. Lancet Oncol 19:76-86, 2018
16. Scher HI, Halabi S, Tannock I, et al: Design and end points of clinical trials for patients with progressive PCa and castrate levels of testosterone: Recommendations of the PCa Clinical Trials Working Group. J Clin Oncol 26:1148-1159, 2008
17. Antonarakis ES, Lu C, Wang H, et al: AR-V7 and resistance to enzalutamide and abiraterone in PCa. N Engl J Med 371:1028-1038, 2014
18. Beltran H, Hruszkewycz A, Scher HI, et al: The role of lineage plasticity in PCa therapy resistance. Clin Cancer Res 25:6916-6924, 2019
19. Khalaf DJ, Annala M, Taavitsainen S, et al: Optimal sequencing of enzalutamide and abiraterone acetate plus prednisone in metastatic castration-resistant PCa: A multicentre, randomised, open-label, phase 2, crossover trial. Lancet Oncol 20:1730-1739, 2019
20. Matsubara N, Yamada Y, Tabata KI, et al: Abiraterone followed by enzalutamide versus enzalutamide followed by abiraterone in chemotherapy-naive patients with metastatic castration-resistant PCa. Clin Genitourin Cancer 16:142-148, 2018
21. Terada N, Maughan BL, Akamatsu S, et al: Exploring the optimal sequence of abiraterone and enzalutamide in patients with chemotherapy-naïve castration-resistant PCa: The Kyoto-Baltimore Collaboration. Int J Urol 24:441-448, 2017

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

TRANSFORMER: A Randomized Phase II Study Comparing Bipolar Androgen Therapy Versus Enzalutamide in Asymptomatic Men With Castration-Resistant Metastatic Prostate Cancer

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Samuel R. Denmeade
Stock and Other Ownership Interests: Sophiris Bio
Consulting or Advisory Role: Sophiris Bio
Travel, Accommodations, Expenses: Sophiris Bio

Neeraj Agarwal
Consulting or Advisory Role: Pfizer, Medivation/Astellas, Bristol-Myers Squibb, AstraZeneca, Nektar, Lilly, Bayer, Foundation One Inc, Pharmacyclics, Foundation Medicine, Astellas Pharma, Exelixis, AstraZeneca, Pfizer, Merck, Novartis, Eisai, Seattle Genetics, EMD Serono, Janssen Oncology, AVEO, Calithera Biosciences, MEI Pharma
Research Funding: Bayer, Bristol-Myers Squibb, GlaxoSmithKline, Takeda, Novartis, Pfizer, BN ImmunoTherapeutics, Exelixis, TRACON Pharma, Rexahn Pharmaceuticals, Amgen, AstraZeneca, Active Biotech, Bavarian Nordic, Calithera Biosciences, Celldex, Eisai, Genentech, Immunomedics, Janssen, Merck, Newlink Genetics, Prometheus, Sanofi

David C. Smith
Research Funding: Agensys, Incyte, Lilly, Novartis, Seattle Genetics, Bristol-Myers Squibb/Medarex, Genentech, Astellas Pharma, Bayer, ESSA, Roche, MedImmune

Michael T. Schweizer
Consulting or Advisory Role: Resverlogix
Research Funding: Janssen, AstraZeneca, Roche, Pfizer, Zenith Epigenetics, Madison Vaccines, Inc., Immunomedics, Bristol-Myers Squibb, Merck, Tmunity Therapeutics, Inc.

Mark N. Stein
Consulting or Advisory Role: Merck Sharp & Dohme, Exelixis, Exelixis, Xencor
Research Funding: Oncoceutics, Merck Sharp & Dohme, Janssen Oncology, Medivation/Astellas, Advaxis, Suzhou Kintor Pharmaceuticals, Harpoon, Bristol-Myers Squibb, Genocea Biosciences, Lilly, Nektar, Seattle Genetics, Xencor, Tmunity Therapeutics, Inc., Exelixis

Vasileios Assikis
Consulting or Advisory Role: Bayer
Speakers' Bureau: AstraZeneca

Przemyslaw W. Twardowski
Honoraria: Astellas Medivation, Bayer, Janssen, Genentech/Roche, Sanofi/Aventis
Consulting or Advisory Role: Sanofi/Aventis, Janssen
Speakers' Bureau: Astellas Pharma, Bayer, Janssen, Genentech, Sanofi

Thomas W. Flaig
Leadership: Aurora Oncology
Stock and Other Ownership Interests: Aurora Oncology
Consulting or Advisory Role: Seattle Genetics, Janssen Oncology
Research Funding: Novartis, Bavarian Nordic, Dendreon, GTx, Janssen Oncology, Medivation, Sanofi, Pfizer, Bristol-Myers Squibb, Roche/Genentech, Exelixis, Aragon Pharmaceuticals, Sotio, Tokai Pharmaceuticals, Astrazeneca/MedImmune, Lilly, Astellas Pharma, Agensys, Seattle Genetics, La Roche-Posay, Merck
Patents, Royalties, Other Intellectual Property: The University of Colorado has filed 2 patents related in which I am an inventor. These are related to early-stage bladder cancer treatment and detection. Neither is commercialized or licensed at this time.

Russell Z. Szmulewitz
Honoraria: Astellas Pharma
Consulting or Advisory Role: AstraZeneca, AbbVie, Exelixis, Merck, Amgen, Janssen Oncology, Sanofi, Astellas Pharma, Pfizer
Research Funding: AbbVie, Astellas Pharma, Incyte, Macrogenics, Janssen Oncology
Patents, Royalties, Other Intellectual Property: Patent licensed by The University of Chicago of which I am a co-inventor to Corcept Therapeutics for combination AR/GR inhibition in prostate cancer
Travel, Accommodations, Expenses: Corcept Therapeutics

Jeffrey M. Holzbeierlein
Consulting or Advisory Role: Basilea
Research Funding: MDxHealth
(OPTIONAL) Uncompensated Relationships: Astellas Medivation

Ralph J. Hauke
Stock and Other Ownership Interests: Aethlon
Research Funding: US Oncology, Bristol-Myers Squibb, Merck, Amgen, Novartis, Exelixis

Guru Sonpavde
Honoraria: UpToDate
Consulting or Advisory Role: Genentech, Merck, Eisai, AstraZenecam, Janssen, Bristol-Myers Squibb, Exelixis, EMD Serono, Astellas Pharma, Bicycle Therapeutics, Pfizer, Seattle Genetics
Speakers' Bureau: Physicans' Education Resource, Onclive, Research to Practice, Medscape
Research Funding: Janssen, Sanofi, AstraZeneca
Travel, Accommodations, Expenses: Bristol-Myers Squibb
Other Relationship: AstraZeneca, Bristol-Myers Squibb, Astellas Pharma, Bavarian Nordic, Debiopharm GroupQED Therapeutics, Elsevier

Jorge A. Garcia
Honoraria: UpToDate, MerckJanssen, Amgen, Bayer, MJH Associates
Consulting or Advisory Role: Sanofi, Bayer, Eisai, Clovis Oncology, Targeted Oncology
Speakers' Bureau: Bayer, Sanofi, MerckSanofi/Aventis
Research Funding: Pfizer, Orion Pharma GmbH, Janssen Oncology, Genentech/Roche, Lilly, Merck
Travel, Accommodations, Expenses: Bayer, Sanofi, Eisai, Medivation/Astellas, Merck, Clovis Oncology, Janssen

Arif Hussain
Consulting or Advisory Role: AstraZeneca, Bayer, Exelixis, Janssen Oncology
Research Funding: Sotio, Merck, Bayer, Clovis Oncology, Pfizer, Constellation Pharmaceuticals, Nektar, Roche/Genentech, Infinity Pharmaceuticals

Oliver Sartor
Stock and Other Ownership Interests: Lilly, GlaxoSmithKline, AbbVie, Cardinal Health, United Health Group, PSMA Therapeutics, Clarity Pharmaceuticals, Noria Therapeutics, Clovis Oncology
Consulting or Advisory Role: Bayer, Sanofi, AstraZeneca, Dendreon, Constellation Pharmaceuticals, Advanced Accelerator Applications, Pfizer, Bristol-Myers Squibb, Bavarian Nordic, EMD Serono, Astellas Pharma, Progenics, Blue Earth Diagnostics, Myovant Sciences, Myriad Genetics, Novartis, Clarity Pharmaceuticals, Fusion Pharmaceuticals, Isotopen Technologien, Janssen, Noxopharm, Clovis Oncology, Noria Therapeutics, Point Biopharma, TeneoBio, Telix Pharmaceuticals, Theragnostics
Research Funding: Sanofi, Endocyte, Merck, InVitae, Constellation Pharmaceuticals, Advanced Accelerator Applications, AstraZeneca, Dendreon, Sotio, Janssen, Progenics
Expert Testimony: Sanofi
Travel, Accommodations, Expenses: Bayer, Johnson & Johnson, Sanofi, AstraZeneca, Progenics

Shifeng Mao
Consulting or Advisory Role: Sanofi, Cardinal Health
Speakers' Bureau: Bristol-Myers Squibb

Michael A. Carducci
Consulting or Advisory Role: Roche/Genentech, Pfizer, Foundation Medicine, Exelixis
Research Funding: Bristol-Myers Squibb, Pfizer, AstraZeneca, EMD Serono, Arcus Biosciences

Mark C. Markowski
Honoraria: Clovis Oncology, Exelixis

Mario A. Eisenberger
Leadership: Veru
Stock and Other Ownership Interests: Veru
Honoraria: Merck Sharp & Dohme, Bristol-Myers Squibb, Seattle Genetics

Emmanuel S. Antonarakis
Honoraria: Sanofi, Dendreon, Medivation, Janssen Biotech, ESSA, Astellas Pharma, Merck, AstraZeneca, Clovis Oncology
Consulting or Advisory Role: Sanofi, Dendreon, Janssen Biotech, ESSA, Merck, AstraZeneca, Clovis Oncology, Lilly, Bayer
Research Funding: Janssen Biotech, Johnson & Johnson, Sanofi, Dendreon, Aragon Pharmaceuticals, Exelixis, Millennium, Genentech, Novartis, Astellas Pharma, Tokai Pharmaceuticals, Merck, AstraZeneca, Clovis Oncology, Constellation Pharmaceuticals
Travel, Accommodations, Expenses: Sanofi, Dendreon, Medivation

No other potential conflicts of interest were reported.

Received: 26 January 2021 | Revised: 2 March 2021 | Accepted: 12 March 2021

DOI: 10.1002/pros.24123

ORIGINAL ARTICLE

The Prostate WILEY

Comparison of germline mutations in African American and Caucasian men with metastatic prostate cancer

Elisa M. Ledet PhD[1] | Earle F. Burgess MD[2] | Alexandra O. Sokolova MD[3] | Ellen B. Jaeger BS[1] | Whitley Hatton MS[1] | Marcus Moses MS[4] | Patrick Miller MPH[1] | Patrick Cotogno MS[1] | Jodi Layton MD[1] | Pedro Barata MD[5] | Brian E. Lewis MD[1] | Mari Nakazawa MD[6] | Jason Zhu MD[2] | Beth Dellinger MS[2] | Sara Elrefai MD[2] | Nellie N. Nafissi MD[7] | Jan B. Egan PhD[8] | Neal Shore MD[9] | Rana R. McKay MD[10] | Alan H. Bryce MD[11] | Heather H. Cheng MD, PhD[3] | Emmanuel S. Antonarakis MD[6] | Oliver Sartor MD[1]

[1]Department of Medicine, Tulane Cancer Center, Tulane University, New Orleans, Louisiana, USA

[2]Genitourinary Oncology Section, Levine Cancer Institute/Atrium Health, Charlotte, North Carolina, USA

[3]Division of Oncology, Department of Medicine, University of Washington Medical Center/Fred Hutchinson Cancer Research Center/VA Puget Sound HCS, Seattle, Washington, USA

[4]School of Medicine, Tulane University, New Orleans, Louisiana, USA

[5]Deming Department of Medicine, Tulane University, New Orleans, Louisiana, USA

[6]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, Maryland, USA

[7]Internal Medicine, Mayo Clinic, Phoenix, Arizona, USA

[8]Center for Individualized Medicine, Mayo Clinic, Scottsdale, Arizona, USA

[9]Carolina Urologic Research Center, Atlantic Urology Clinics, Myrtle Beach, South Carolina, USA

[10]Moores Cancer Center, University of California San Diego, La Jolla, California, USA

[11]Division of Hematology/Oncology, Mayo Clinic Cancer Center, Mayo Clinic, Phoenix, Arizona, USA

Correspondence
Oliver Sartor, MD, Tulane University School of Medicine, 1430 Tulane Ave, Box 8642, New Orleans, LA 70112, USA.
Email: osartor@tulane.edu

Funding information

NCI Cancer Center Support, Grant/Award Number: 5P30 CA006973-52; PNW SPORE, Grant/Award Number: CA097186; U.S. Department of Defense, Grant/Award Numbers: W81XWH-16-PCRP-CCRSA, W81XWH-17-2-0043; National Institutes of Health, Grant/Award Numbers: CA015704, R01 CA238384

Abstract

Background: The goal of this study is to evaluate germline genetic variants in African American men with metastatic prostate cancer as compared to those in Caucasian men with metastatic prostate cancer in an effort to understand the role of genetic factors in these populations.

Methods: African American and Caucasian men with metastatic prostate cancer who had germline testing using multigene panels were used to generate comparisons. Germline genetic results, clinical parameters, and family histories between the two populations were analyzed.

Results: A total of 867 patients were included in this retrospective study, including 188 African American and 669 Caucasian patients. There was no significant difference in the likelihood of a pathogenic or likely-pathogenic variants (PV/LPVs) between African American and Caucasian patients ($p = .09$). African American patients were more likely to have a variant of unknown significance than Caucasians (odds ratio [OR] = 1.95; $p < .0001$). BRCA1 PV/LPVs were higher in African Americans (OR = 4.86; $p = .04$). African American patients were less likely to have a PV/LPV in non-BRCA DNA repair genes (OR = 0.30; $p = .008$). Family history of breast (OR = 2.09; $p = .002$) or ovarian cancer (OR = 2.33; $p = .04$) predicted PV/LPVs in Caucasians but not African-Americans. This underscores the limitations of family history in AA men and the importance of personal history to guide germline testing in AA men.

Conclusions: In metastatic prostate cancer patients, PV/LPVs of tested genes did not vary by race, BRCA1 PV/LPVs were more common in the African American subset. However, PV/LPVs in non-BRCA DNA repair genes were less likely to be encountered in African Americans. Family history associated with genetic testing results in Caucasians only.

KEYWORDS

African American, genetics, germline, metastatic prostate cancer, pathogenic variants, racial disparity

1 | INTRODUCTION

Racial disparity has been a persistent and challenging problem in prostate cancer research despite ongoing efforts. African American men are at higher risk of prostate cancer and approximately twofold higher risk of dying from prostate cancer compared to other racial or ethnic groups (1, 2). For African Americans there are significant differences in screening and treatment patterns, enrollment in clinical trials, outcomes, limited understanding of tumor biology and biomarker utility specific to African American patients.[1–8] Similar to race, family history is also a potent risk factor for prostate cancer. The inherited risk of prostate cancer is estimated to be as high as 60% and men with a first degree relative (FDR) with prostate cancer have been reported to be twice as likely to develop this disease.[9] While risk factors such as family history and race have been well characterized, much remains unknown about how genetic factors influence risk in African Americans with prostate cancer. To date, African American men have been underrepresented in germline genetic studies of prostate cancer.[8,10]

Studies in advanced prostate cancer have been conducted primarily on Caucasian/European cohorts, and these studies have highlighted the prevalence and clinical significance of germline alterations. For example, Pritchard, et al.[11] showed that pathogenic/likely pathogenic germline variants (PV/LPV) in DNA repair genes were present in 11.8% of patients with metastatic prostate cancer. Patients with selected DNA repair germline PV/LPV not only have an increased risk of developing cancer, but a number of mutations are associated with a poor prognosis. Importantly, patients with germline *BRCA1* and *BRCA2* pathogenic mutations and metastatic prostate cancer may respond better to PARP inhibitors and platinum-based chemotherapy.[12–14] Specifically, patients with mCRPC and *BRCA1* or *BRCA2* alterations had significantly longer progression free and overall survival with olaparib, compared to those treated with abiraterone or enzalutamide. The benefit of PARP inhibitors may be extended to patients with selected alterations detected in other homologous recombination repair genes.[15] Both olaparib and rucaparib are now Food and Drug Administration (FDA) approved for treatment of mCRPC and both approvals specifically note germline *BRCA1/2* mutations. Studies have shown that mismatch repair gene status in tumors predicts for a positive therapeutic response to PD-1 inhibitors[16] and pembrolizumab was FDA-approved in 2018.

In a cross-sectional study of 3607 men with prostate cancer, 17.2% ($n = 620$) were found to have pathogenic or likely pathogenic germline variants. Age, race, and family history did not correlate with positive test results though these clinical data were quite limited. Only 227 (~6%) of the men tested were African American. African Americans had lower rates of positive variants compared to other ethnic groups (odds ratio [OR] = 0.527; $p = .006$).[17] In a study focusing on a subset of well characterized genes, African American patients with prostate cancer had significantly fewer germline alterations compared to Caucasians (7.5% vs. 13.9%, respectively).[18] This study was problematic because clinical data were limited. Kwon et al.[19] had a variety of ethnic groups in a large analysis but only 41 patients were of African ancestry. Taken together studies of germline PV/LPV in African American men remain suboptimal.

ELAC/HPC2,[20] *MSR1*,[21] *CHEK2*[22], and *EPHB2*[23] have been reported in association with prostate cancer risk in African American men but await confirmatory studies. Multiple linkage and GWAS studies have linked the 8q24 region with prostate cancer; these risk SNPs are

relatively small in magnitude of effect and the underlying etiology of noncoding changes remains under study.[24–26] Though these associations have been identified in African American patients with prostate cancer, reproducible causal or risk genes have not been identified and current gene panels used for germline genetic testing are primarily derived from variants identified in other ethnicities. Given the underrepresentation in clinical genetic testing and research, and the clinical importance, for patients and their families, it is especially critical to better understand racial disparity with respect to germline PV/LPV data.

Given the notable paucity of germline data on African American men, especially those with advanced prostate cancer, the goal of the present study is to evaluate germline alterations in African American men, all of whom had documented metastatic prostate cancer. Ultimately, understanding the landscape of germline variants in African Americans, with concomitant clinical cofactors and family history, is critical for understanding and reducing health care disparities.

2 | MATERIALS AND METHODS

2.1 | Patient cohort

African American and Caucasian men with metastatic prostate cancer were recruited from seven sites including Tulane University Cancer Center, Levine Cancer Institute/Carolinas Medical Center, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, University of Washington, Mayo Clinic, and Atlantic Urology Clinics. All patients in this cohort had distant metastatic disease, confirmed by radiographic imaging, and all had germline genetic testing. In addition to germline testing results, clinical data including self-reported race, Gleason score, age at diagnosis, clinical staging, and self-reported cancer family history were retrospectively compiled from medical records. All clinical data were deidentified before analyses under Tulane University IRB protocol number 2019-329 which waived the requirement to obtain written patient informed consent.

2.2 | Germline panel composition and testing

Patients in this cohort had prior germline testing with a commercially available clinical panel between 2015 and 2020. Institutions used a variety of germline panels evaluating germline alterations in 12–86 cancer-associated genes. The panels utilized included: Invitae Multi-Cancer panel ($N = 645$) (Invitae), Color Hereditary Cancer panel ($N = 183$) (Color Genomics), Myriad MyRisk panel ($N = 7$) (Myriad Genetics), BROCA panel ($N = 6$) (UW Medical Center), and other commercial panels ($N = 16$). Variants were evaluated and subjected to clinical interpretation using American College of Medical Genetics and Genomics criteria.[27] According to the results reported by each commercial panel, variants interpreted as pathogenic (PV) or likely-pathogenic (LPV) were considered positive and have previously been established to have pathogenic consequences. Variants of unknown significance (VUS) were also identified using standard classification procedures.

TABLE 1 Demographics of the metastatic prostate cancer population tested

	African American	Caucasian
Median age of diagnosis	60 (40–82)	63 (42–93)
Median age at time of germline testing	68 (40–89)	69 (43–93)
Gleason score		
<7	6% ($n = 9$)	6% ($n = 26$)
=7	34% ($n = 50$)	28% ($n = 125$)
>7	58% ($n = 87$)	67% ($n = 301$)
Metastatic at diagnosis	44% ($n = 65$)	37% ($n = 136$)

2.3 | Statistical analysis

The χ^2 test and confidence intervals were calculated using SAS 9.7 (SAS). To compare proportions between groups when the number of occurrences in a cell were fewer than 5, the Fisher exact test was used. The p values less than .05 were considered significant. These tests were used to assess associations between genetic alterations and clinical variables including race and family history. To accommodate the diversity of genetic panels and institutions, for individual gene analyses, patients were excluded if the panel used for germline testing did not include the given gene of interest.

3 | RESULTS

3.1 | Study population

A total of 867 patients were included in this retrospective study. This included 188 African American patients and 669 Caucasian patients (see Table 1 and Table S1); all patients had radiographic positive metastatic prostate cancer. The median age at diagnosis was 60 years (range = 40–82) for African Americans and 63 years (range = 42–93) for Caucasians. At the time of germline testing, the median age for African Americans was 68 years (range = 40–89) and 69 years (range = 43–93) for Caucasians. In African Americans, 6% ($n = 9$) had a Gleason score of less than 7, 34% ($n = 50$) had a Gleason score of 7, and 58% ($n = 87$) had a Gleason score more than 7. In Caucasians, 6% ($n = 26$) had a Gleason score of less than 7, 28% ($n = 125$) had a Gleason score of 7, and 67% ($n = 301$) had a Gleason score of more than 7. 44% of African Americans ($n = 65$) were metastatic at diagnosis compared to 37% of Caucasians ($n = 136$). No statistically significant differences between the African American and Caucasian groups were seen in terms of age at diagnosis, age at testing, Gleason scores, or metastatic disease at diagnosis.

TABLE 2 Germline variants detected

	Negative	PV/LPV	PV/LPV + VUS	VUS	Total
African American	35.1% (*n* = 66)	5.3% (*n* = 10)	4.3% (*n* = 8)	55.3% (*n* = 104)	188
Caucasian	48.9% (*n* = 327)	8.1% (*n* = 54)	6.4% (*n* = 43)	36.6% (*n* = 245)	669
Unknown	50% (*n* = 5)	30% (*n* = 3)	0% (*n* = 0)	20% (*n* = 20)	10
Grand total	44.4% (*n* = 385)	9.2% (*n* = 80)	5.8% (*n* = 51)	40.5% (*n* = 351)	867

Abbreviations: LPV, likely-pathogenic variants; PV, pathogenic variants.

3.2 | Pathogenic, likely-pathogenic, and VUS

In the African American patients, 6% of patients (*n* = 11) had a PV/LPV, 55% of patients (*n* = 104) had a VUS, 4% of patients (*n* = 8) had both a PV/LPV and VUS, and 35% of patients had no PV/LPV or VUS reported (*n* = 65) (Table 2). For Caucasians, 10% of patients (*n* = 66) had a PV/LPV germline alteration, 37% of patients (*n* = 245) had a VUS, 6% of patients (*n* = 43) had both a PV/LPV and VUS, and 47% of patients had no germline alterations (*n* = 315). Overall, there was no significant difference in the likelihood of a PV/LPV between African American and Caucasian patients (*p* = .09). African American patients were more likely to have a VUS than Caucasians (OR = 1.95; 95% confidence interval [CI [1.40, 2.71]; *p* < .0001).

Each gene represented on a germline panel was compared between African American and Caucasian patients with metastatic prostate cancer (Table S2). Of the genes evaluated, African Americans were more likely to have a *BRCA1* PV/LPV (OR = 4.86; 95% CI [1.08, 21.93]; *p* = .04), however, we note the small number of cases as a limitation. There were no other PV/LPVs detected which were significantly different between African American and Caucasian patients. Among VUSs, VUS in *BRCA2* (*p* = .04), *PALB2* (*p* = .0007), and *PTCH1* (*p* = .03) were more frequent in African Americans compared to Caucasians. There were no other gene specific VUSs which were significantly different between African Americans and Caucasians (Table S3).

Next, functionally related genes were evaluated as a group (Tables 3–5). African American patients were substantially less likely to have a PV/LPV in any non-*BRCA* gene (OR = 0.27; 95% CI [0.12, 0.64]; *p* = .0008). Additionally, African American patients were less likely to have a PV/LPV in a non-BRCA DNA repair gene (*MSH2*, *MSH6*, *PMS2*, *MLH1*, *ATM*, *RAD50*, *RAD51D*, *NBN*, *CHEK2*, *BRIP1*, *PALB2*, *RAD51C*, *ATM*, *BLM*, and *TP53*) (OR = 0.30; 95% CI [0.11, 0.85]; *p* = .008). Among all DNA repair genes analyzed herein (including *BRCA1* and *BRCA2)* there was no significant difference between African American and Caucasian patients (*p* = .29).

3.3 | Family history

Cancer family history was collected from patient charts (see Tables S4, S5, S6, and S7). Among these prostate cancer patients, PV/LPV findings were more likely in Caucasians with at least one FDR with ovarian cancer (OR = 2.33; 95% CI [1.05, 5.17]; *p* = .04). However, there was no significant difference in the frequency of PV/LPV alterations in African Americans with FDR with ovarian cancer (OR = 6.33; 95% CI [0.98, 40.76]; *p* = .08). There was no significant difference in the frequency of PV/LPVs in African Americans (*p* = .12) or Caucasians (*p* = .33) with at least one FDR with prostate cancer. In Caucasians, PV/LPV germline alterations were more likely with at least one FDR with breast cancer (OR = 2.09; 95% CI [1.31, 3.32]; *p* = .002). However, there were no significant difference in the frequency of PV/LPV alterations in African Americans with at least one FDR with breast cancer (OR = 2.15; 95% CI [0.75, 6.19]; *p* = .21). There was no significant difference in the frequency of PV/LPV alterations in Caucasians (*p* = .80) with at least one FDR with pancreatic cancer. None of the African American patients reported a family history of pancreatic cancer.

4 | DISCUSSION

These findings highlight the importance of testing and expanding access to testing especially for African American patients with metastatic prostate cancer. We did not find any overall differences in the frequency of PV/LPVs between African Americans and Caucasians in this population of men with metastatic prostate cancer. However, African American patients were less likely to have a PV/

TABLE 3 PV/LPV in any non-BRCA gene

PV/LPV non-BRCA gene	African American	Caucasian	OR	*p* Value	95% CI
Yes	3% (*n* = 6)	11% (*n* = 72)	0.2749	.0008	0.1176, 0.6426
No	97% (*n* = 181)	89% (*n* = 597)			

Abbreviations: CI, confidence interval; LPV, likely-pathogenic variants; OR, odds ratio; PV, pathogenic variants.

TABLE 4 PV/LPV in DNA-repair genes (*BRCA1*, *BRCA2*, *MSH2*, *MSH6*, *PMS2*, *MLH1*, *ATM*, *RAD50*, *RAD51D*, *NBN*, *CHEK2*, *BRIP1*, *PALB2*, *RAD51C*, *ATM*, *BLM*, and *TP53*)

PV/LPV DNA repair genes	African American	Caucasian	OR	*p* Value	95% CI
Yes	9% (*n* = 16)	12% (*n* = 77)	0.7152	.2887	0.4066, 1.2579
No	91% (*n* = 172)	88% (*n* = 592)			

Abbreviations: CI, confidence interval; LPV, likely-pathogenic variants; OR, odds ratio; PV, pathogenic variants.

TABLE 5 PV/LPV in non-BRCA DNA repair genes (*MSH2*, *MSH6*, *PMS2*, *MLH1*, *ATM*, *RAD50*, *RAD51D*, *NBN*, *CHEK2*, *BRIP1*, *PALB2*, *RAD51C*, *ATM*, *BLM*, and *TP53*)

PV/LPV non-BRCA DNA repair gene	African American	Caucasian	OR	*p* Value	95% CI
Yes	2% (*n* = 4)	7% (*n* = 45)	0.3014	.00836	0.107, 0.8493
No	98% (*n* = 184)	93% (*n* = 624)			

Abbreviations: CI, confidence interval; LPV, likely-pathogenic variants; OR, odds ratio; PV, pathogenic variants.

LPV in any non-*BRCA* genes and in non-*BRCA* DNA repair genes. African Americans were more likely to have a PV/LPV *BRCA1* compared to their Caucasian counterparts.

African Americans in this study had a significantly higher overall incidence of germline VUSs. In a gene specific analysis, VUS alterations in *BRCA2*, *PALB2*, and *PTCH1* were more frequently detected in African Americans compared to Caucasians. Unlike PV/LPV, for any given VUS, by definition, there is insufficient evidence to determine whether or not a mutation is detrimental or contributes to cancer risk. In African Americans, the significantly increased detection of VUSs likely reflects a bias in variant classification of genes, which relies on patient data primarily assembled and validated from Caucasian cohorts. Importantly, this bias may also extend to PV/LPVs and may account for the overall lower frequency of pathogenic variants in this African American cohort. Regardless of the pathogenicity of individual VUSs, the higher frequency of VUSs in African Americans indicates that this population may be underrepresented in population data utilized in identifying variants. This underrepresentation may be especially critical for germline variants in prostate cancer given the high significantly higher incidence of prostate cancer in African Americans. More data are necessary to further classify these VUS into pathogenic or non-pathogenic categories.

The higher frequency of *BRCA1* in African Americans with metastatic prostate cancer is notable given the recent FDA approvals of olaparib and rucaparib for patients with germline *BRCA1* or *BRCA2*. These data emphasize the importance of improving access to genetic counseling and germline genetic testing for inherited cancer risk for African American men with advanced prostate cancer. Similarly, when comparing somatic tumor DNA from metastatic prostate cancer in African Americans and Caucasians, there were more tumoral *BRCA1* mutations in African Americans (4%) compared to Caucasians (1%).[28] We are cautious to note that conclusions need replication in larger data sets before they can be considered definitive.

Guidelines reliant on family history have a number of shortcomings and current National Comprehensive Cancer Network guidelines are not reliant on family history alone. It is well known that family history is incomplete for many, and even important genes have incomplete penetrance. Herein, however, family history was associated with PV/LPV in several selected Caucasian populations but not in African Americans. Caucasians but not African Americans with a FDR with breast or ovarian cancer (but not prostate cancer) were more likely to have a PV/LPV. This may or may not reflect differences in recall, family structure, health communication, and genetic dependency, as well a smaller sample sizes resulting in a relatively under-powered assessment in the African American dataset.

While this study included a large number of metastatic prostate cancer patients there were significant limitations. A larger sample size is needed to optimally assess the germline landscape in this population. Additionally, it is possible that the current gene panels are incomplete when it comes to important genes associated with prostate cancer, especially in African Americans. This was a retrospective study of metastatic prostate cancer patients and testing biases are possible. We have not tracked how many patients refused to undergo testing. Clinical practices at different institutions may have varied in unknown manners. Though most of the genes tested, especially DNA-repair genes, were the same across panels, there were clear variations in other cancer related genes in accordance with what panel was used. This is a limitation of the study. Similarly, the number of genes included on the panels varied. While this was taken in to account for the present analyses for individual genes, optimally all patients should have been tested with a standardized gene panel. This study was also limited to self-reported data for both race and family history. Similarly, since this is a multi-institutional study, genetic variability attributable to geographic factors may also be a limitation.

More access to clinical genetic testing and more research opportunities are needed to address disparities and underrepresentation of African American prostate cancer patients. Further studies are critical for understanding the germline genetic components contributing to disparities in prostate cancer risk and prostate cancer outcomes.

CONFLICT OF INTERESTS

Dr. Sartor has research funding to his institution from AAA, AstraZeneca, Bayer, Merck, Endocyte, Progenics, Novartis, and Janssen. Dr. Sartor has received consulting fees from Astellas, Blue Earth Diagnostics, EMD Serono, Pfizer, Constellation, Dendreon, Bristol-Myers Squibb, Invitae, Merck, Innocrin, Sotio, AAA, AstraZeneca, Bayer, Endocyte, Progenics, Novartis, Janssen, Astellas, Blue Earth Diagnostics, EMD Serono, Pfizer, Constellation, Noria Therapeutics, Clovis, Myriad, Noxopharm, Point Biopharm, Tenebio, Theragnostics, Telix, Clarity Pharmaceuticals, and Fusion. Dr. Shore has research support and consulting fees for AbbVie, Amgen, Astellas, Astra Zeneca, Bayer, BMS, Dendreon, Exact Sciences, Fergene, Foundation Medicine, Invitae, Janssen, Merck, Myriad, Pfizer, and Sanofi, Tolmar. Dr. Cheng receives funding from PNW SPORE CA097186, DOD W81XWH-17-2-0043, NIH CA015704, Prostate Cancer Foundation; research funding to her institution from Clovis, Janssen, Sanofi, Medivation/Astellas, Color Foundation, and consulting fees from AstraZeneca. Dr. Antonarakis has served as a paid consultant/advisor for Invitae, Janssen, Pfizer, Sanofi, Dendreon, Merck, Bristol-Myers Squibb, AstraZeneca, Clovis, Bayer, Constellation, Eli Lilly and Amgen; and has received research funding to his institution from Janssen, Johnson & Johnson, Sanofi, Dendreon, Genentech, Novartis, Bayer, Merck, Bristol-Myers Squibb, AstraZeneca, ESSA and Constellation. Additionally, Dr. Antonarakis is partially supported by the Patrick Walsh Prostate Cancer Research Fund, the Prostate Cancer Foundation, the NCI Cancer Center Support Grant 5P30 CA006973-52, the NIH grant R01 CA238384, and the DOD Clinical Consortium award W81XWH-16-PCRP-CCRSA. Dr. Bryce received honoraria from Foundation Medicine, Novartis, Astellas, and Merck. Dr. McKay has served as a paid consultant for Janssen, Novartis, Tempus, Exelixis, Pfizer, Bristol-Myers Squibb, Astellas Medivation, Dendreon, Vividion Therapeutics, Bayer and has research funding to her institution from Pfizer and Bayer. Dr. Burgess has received consulting fees from Johnson and Johnson, honoraria from Exelixis and Bayer, and research funding to his institution from Pfizer and Astellas Pharma. Dr. Zhu has served as a paid consultant for NGM Biopharmaceuticals and Bayer. All other authors have no conflict of interests to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Elisa M. Ledet https://orcid.org/0000-0003-1230-3255
Nellie N. Nafissi https://orcid.org/0000-0003-0436-5931
Alan H. Bryce https://orcid.org/0000-0002-0206-3895
Heather H. Cheng https://orcid.org/0000-0002-1365-0702
Emmanuel S. Antonarakis https://orcid.org/0000-0003-0031-9655
Oliver Sartor https://orcid.org/0000-0002-8777-7343

REFERENCES

1. McGinley KF, Tay KJ, Moul JW. Prostate cancer in men of African origin. *Nat Rev Urol*. 2016;13(2):99-107.
2. Tsodikov A, Gulati R, de Carvalho TM, et al. Is prostate cancer different in black men? Answers from 3 natural history models. *Cancer*. 2017;123(12):2312-2319.
3. Holmes JA, Bensen JT, Mohler JL, Song L, Mishel MH, Chen RC. Quality of care received and patient-reported regret in prostate cancer: analysis of a population-based prospective cohort. *Cancer*. 2017;123(1):138-143.
4. Wissing MD, Kluetz PG, Ning YM, et al. Under-representation of racial minorities in prostate cancer studies submitted to the US Food and Drug Administration to support potential marketing approval, 1993-2013. *Cancer*. 2014;120(19):3025-3032.
5. Leapman MS, Freedland SJ, Aronson WJ, et al. Pathological and Biochemical Outcomes among African-American and Caucasian Men with Low Risk Prostate Cancer in the SEARCH Database: implications for active surveillance candidacy. *J Urol*. 2016;196(5):1408-1414.
6. Ahaghotu C, Tyler R, Sartor O. African American Participation in Oncology Clinical Trials—Focus on Prostate Cancer: implications, barriers, and potential solutions. *Clin Genitourin Cancer*. 2016;14(2):105-116.
7. Eggly S, Hamel LM, Heath E, et al. Partnering around cancer clinical trials (PACCT): study protocol for a randomized trial of a patient and physician communication intervention to increase minority accrual to prostate cancer clinical trials. *BMC Cancer*. 2017;17(1):807.
8. Spratt DE, Chan T, Waldron L, et al. Racial/ethnic disparities in genomic sequencing. *JAMA Oncology*. 2016;2(8):1070-1074.
9. Hjelmborg JB, Scheike T, Holst K, et al. The heritability of prostate cancer in the Nordic Twin Study of Cancer. *Cancer Epidemiol Biomarkers Prev*. 2014;23(11):2303-2310.
10. Rogers CR, Rovito MJ, Hussein M, et al. Attitudes toward genomic testing and prostate cancer research among Black Men. *Am J Prev Med*. 2018;55(5S1):S103-S111.
11. Pritchard CC, Offit K, Nelson PS. DNA-repair gene mutations in metastatic prostate cancer. *N Engl J Med*. 2016;375(18):1804-1805.
12. Fong PC, Boss DS, Yap TA, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. *N Engl J Med*. 2009;361(2):123-134.
13. Kaufman B, Shapira-Frommer R, Schmutzler RK, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. *J Clin Oncol*. 2015;33(3):244-250.
14. Yang D, Khan S, Sun Y, et al. Association of BRCA1 and BRCA2 mutations with survival, chemotherapy sensitivity, and gene mutator phenotype in patients with ovarian cancer. *JAMA*. 2011;306(14):1557-1565.
15. de Bono J, Mateo J, Fizazi K, et al. Olaparib for metastatic castration-resistant prostate cancer. *N Engl J Med*. 2020;382(22):2091-2102.
16. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med*. 2015;372(26):2509-2520.
17. Nicolosi P, Ledet E, Yang S, et al. Prevalence of germline variants in prostate cancer and implications for current genetic testing guidelines. *JAMA oncology*. 2019;5(4):523-528.
18. Sartor O, Yang S, Ledet E, Moses M, Nicolosi P. Inherited DNA-repair gene mutations in African American men with prostate cancer. *Oncotarget*. 2020;11(4):440-442.
19. Kwon DH, Borno HT, Cheng HH, Zhou AY, Small EJ. Ethnic disparities among men with prostate cancer undergoing germline testing. *Urol Oncol*. 2020;38(3):80 e81-80 e87.
20. Robbins CM, Hernandez W, Ahaghotu C, et al. Association of HPC2/ELAC2 and RNASEL non-synonymous variants with prostate cancer risk in African American familial and sporadic cases. *Prostate*. 2008;68(16):1790-1797.
21. Wallace TA, Martin DN, Ambs S. Interactions among genes, tumor biology and the environment in cancer health disparities: examining the evidence on a national and global scale. *Carcinogenesis*. 2011;32(8):1107-1121.

22. Southey MC, Goldgar DE, Winqvist R, et al. PALB2, CHEK2 and ATM rare variants and cancer risk: data from COGS. *J Med Genet*. 2016; 53(12):800-811.
23. Robbins CM, Hooker S, Kittles RA, Carpten JD. EphB2 SNPs and sporadic prostate cancer risk in African American men. *PLoS One*. 2011; 6(5):e19494.
24. Gudmundsson J, Sulem P, Manolescu A, et al. Genome-wide association study identifies a second prostate cancer susceptibility variant at 8q24. *Nature Genet*. 2007;39(5):631-637.
25. Yeager M, Chatterjee N, Ciampa J, et al. Identification of a new prostate cancer susceptibility locus on chromosome 8q24. *Nature Genet*. 2009;41(10):1055-1057.
26. Matejcic M, Saunders EJ, Dadaev T, et al. Germline variation at 8q24 and prostate cancer risk in men of European ancestry. *Nat Commun*. 2018;9(1):4616.
27. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17(5):405-424.
28. Mahal BA, Alshalalfa M, Kensler KH, et al. Racial differences in genomic profiling of prostate cancer. *N Engl J Med*. 2020; 383(11):1083-1085.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Ledet EM, Burgess EF, Sokolova AO, et al. Comparison of germline mutations in African American and Caucasian men with metastatic prostate cancer. *The Prostate*. 2021;81:433-439. https://doi.org/10.1002/pros.24123

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Editorial

Referring to the article published on pp. 295–303 of this issue

Molecular Subtyping in the Neoadjuvant Setting in Prostate Cancer: Envisioning the Possibilities

Heather H. Cheng [a,b,*]

[a] *Department of Medicine, Division of Oncology, University of Washington, Seattle, WA, USA*

[b] *Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA*

A persistent clinical challenge is that approximately half of men diagnosed with high-risk localized prostate cancer experience recurrence. In other solid tumor cancers, neoadjuvant therapy for localized disease reduces the risk of recurrence and is the standard of care. Despite studies investigating intensive androgen deprivation therapy (ADT) and ADT in combination with docetaxel [1–3], this approach has not been standard for prostate cancer. Molecular subtyping, which has seen major advances in metastatic prostate cancer, may add value to stratification and better treatment selection in the high-risk localized disease setting.

It has been 5 yr since the discoveries that DNA damage repair (DDR) genes are altered in up to a quarter of metastatic castration-resistant prostate cancers [4] and that inherited (germline) DDR (gDDR) gene alterations occur in 11.8% of men with metastatic prostate cancer, higher than the rate in localized disease and among men without cancer [5]. Men who carry germline *BRCA1/2* mutations and develop prostate cancer have more aggressive disease and worse outcomes than men without these mutations [6]. Thus, men with gDDR alterations, including in *BRCA1/2*, may be at the highest risk of disease recurrence and may benefit most from neoadjuvant treatment approaches. In addition, the PARP inhibitors rucaparib and olaparib have been approved by the US Food and Drug Administration for metastatic castration-resistant prostate cancer associated with germline and/or somatic *BRCA1/2* mutations, and in the case of olaparib, a longer list of DDR gene alterations for treatment candidacy.

We have needed more data informing prevalence of gDDR alterations in men with unfavorable intermediate-risk or high-risk localized disease. There are other key questions regarding prostate cancers arising in the context of gDDR alterations. What is the response to inhibition of androgen receptor (AR) signaling in localized disease? What is the response to DNA-damaging agents (PARP inhibition, platinum chemotherapy)? Would sequential or combination approaches be more effective?

Some key answers are reported in this issue of *European Urology* by Berchuck et al [7] in their manuscript on the impact of pathogenic gDDR alterations on response to intense neoadjuvant androgen deprivation therapy (ADT). The study was a retrospective analysis of 201 patients pooled from five completed, prospective neoadjuvant trials of intensive neoadjuvant ADT in the setting of high-risk localized prostate cancer. The authors report 9.5% (19/201) of the men had pathogenic gDDR variants, with *BRCA2* (n = 6) and *ATM* (n = 4) being the most common; others included *BRCA1*, *CHEK2*, *RAD50*, *RAD51D*, *MSH6*, and *PMS2*. Patients with and without gDDR alterations achieved similar rates of exceptional pathologic complete response (defined as pathologic complete response of cancer or minimal residual disease) of 26% versus 22%. The 3-yr biochemical recurrence–free survival was 45% (95% confidence interval [CI] 7.9–78%) among men with gDDR alterations compared to 55% (95% CI 44–64%) for men not found to have gDDR alterations. While the absolute numbers are small, the findings are impactful.

A strength of this study is its freedom from skewing due to ascertainment biases; simply put, the five studies were largely conducted in an era before our current knowledge of gDDR mutations in prostate cancer. As awareness of germline variants increases, so will self-selection and proportional

DOI of original article: https://doi.org/10.1016/j.eururo.2021.03.031.
* Division of Medical Oncology, University of Washington, 825 Eastlake Avenue East, Seattle, WA 98109, USA. E-mail address: hhcheng@uw.edu.

https://doi.org/10.1016/j.eururo.2021.04.029

skewing in prospective studies, particularly between studies that are selected versus unselected for specific alterations. Thus, these findings serve as important supportive evidence for NCCN prostate cancer guideline recommendation to offer germline testing and genetic counseling to men with a personal history of high-risk localized prostate cancer [8] and as a foundation for planning future studies.

An acknowledged and important limitation is the absence of tumors for somatic evaluation; this is the result of a lack of available pretreatment biopsies and the fact that pathologic responses may leave insufficient residual tumor for next-generation sequencing and other studies (an ironic consequence of success). The makes it impossible to identify somatic-only alterations in DDR genes among the non-gDDR comparator group, so there may be a subset of DDR-deficient tumors (without germline association) within the non-gDDR comparator group that could . The absence of tumor also precludes a deeper examination of the non-*BRCA2* genes, that is, the rarer and/or moderate-penetrance genes (eg, *ATM, CHEK2, BRCA1, RAD50*). For these genes, evaluation of second allele inactivation, functional studies, and newer molecular profiling techniques may provide evidence about whether a given germline variant is more central or peripheral to the tumor biology. Future neoadjuvant studies will hopefully incorporate systematic collection of diagnostic biopsies in addition to surgical specimens.

Importantly, for patients with gDDR alterations and intermediate- or high-risk localized disease, there was not an obvious was not an inferior response to neoadjuvant intensive ADT, although the results were shy of statistical signifiance.more nu. More studies are needed to follow up on this observation, which mirrors those in the metastatic setting, in which AR-targeting agents in aggregate do to demonstrate in total inferior responses for patients with gDDR alterations [9,10]. Thus, there remains a strong rationale to pursue neoadjuvant approaches in men with gDDR alterations who have localized prostate cancer, whether with intensive ADT or ADT in combination with DNA-damaging agents such as platinum chemotherapy or PARP inhibitors. Indeed, there are trials ongoing and in development, such as the PROTEUS study (NCT03767244), a niraparib study (NCT04030559), the GUNS study (NCT04812366), and others. Dedicated De genetic registries such as PROMISE (www.prostatecancerpromise.org) will help facilitate identification of carriers of gDDR alterations for trial efforts, and together with long term follow-up, will foster collaborative learning about biology and treatment outcomes in prostate cancers arising in the context of the rare and ultra-rare germline mutations and variants.

In summary, Berchuck, Taplin, and their colleagues report a 9.5% prevalence of gDDR alterations in a pooled, unselected cohort of men with intermediate- and high-risk prostate cancer, justifying the NCCN prostate guideline recommendation to offer men with high-risk localized disease germline genetic testing and the additional studies investigating neoadjuvant ADT-based approaches for this patient population. Finally, the view for the future is more widespread identification of men who carry gDDR alterations earlier in the disease course, ideally soon after or even before a prostate cancer diagnosis. This could facilitate options for molecularly informed definitive treatment—perhaps with effective neoadjuvant approaches—and hopefully an overall reduction in the number and proportion of men who carry gDDR alterations who develop metastatic prostate cancer. That would be the kind of skewing we could all get behind.

Conflicts of interest: The author has received research funding from Clovis, Janssen, Sanofi, Medivation/Astellas, and Color Foundation, and has acted in a consulting or advisory role for AstraZeneca and Janssen.

Acknowledgments: The author's work is supported by NIH grants CA097186 and CA015704, CDMRP grant W81XWH-17-2-0043, the Prostate Cancer Foundation, the Institute for Prostate Cancer Research, and Advancing Cancer Treatment.

References

[1] McKay RR, Montgomery B, Xie W, et al. Post prostatectomy outcomes of patients with high-risk prostate cancer treated with neoadjuvant androgen blockade. Prostate Cancer Prostat Dis 2018;21:364–72.

[2] Taplin ME, Montgomery B, Logothetis CJ, et al. Intense androgen-deprivation therapy with abiraterone acetate plus leuprolide acetate in patients with localized high-risk prostate cancer: results of a randomized phase II neoadjuvant study. J Clin Oncol 2014;32:3705–15.

[3] Eastham JA, Heller G, Halabi S, et al. Cancer and Leukemia Group B 90203 (Alliance): radical prostatectomy with or without neoadjuvant chemohormonal therapy in localized, high-risk prostate cancer. J Clin Oncol 2020;38:3042–50.

[4] Robinson D, Van Allen EM, Wu YM, et al. Integrative clinical genomics of advanced prostate cancer. Cell 2015;161:1215–28.

[5] Pritchard CC, Mateo J, Walsh MF, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med 2016;375:443–53.

[6] Castro E, Goh C, Olmos D, et al. Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. J Clin Oncol 2013;31:1748–57.

[7] Berchuck JE, Zhang Z, Silver R, et al. Impact of pathogenic germline DNA damage repair alterations on response to intense neoadjuvant androgen deprivation therapy in high-risk localized prostate cancer. Eur Urol 2021;80:295–303.

[8] National Comprehensive Cancer Network. NCCN prostate cancer guidelines version 1. www.nccn.org/professionals/physician_gls/pdf/prostate.pdf2021

[9] Antonarakis ES, Lu C, Luber B, et al. Germline DNA-repair gene mutations and outcomes in men with metastatic castration-resistant prostate cancer receiving first-line abiraterone and enzalutamide. Eur Urol 2018;74:218–25.

[10] Castro E, Romero-Laorden N, Del Pozo A, et al. PROREPAIR-B: a prospective cohort study of the impact of germline DNA repair mutations on the outcomes of patients with metastatic castration-resistant prostate cancer. J Clin Oncol 2019;37:490–503.

Received: 24 June 2021 | Accepted: 30 August 2021

DOI: 10.1002/pros.24236

ORIGINAL ARTICLE

The Prostate WILEY

Efficacy of systemic therapies in men with metastatic castration resistant prostate cancer harboring germline *ATM* versus *BRCA2* mutations

Alexandra O. Sokolova MD[1] | Catherine H. Marshall MD, MPH[2] | Rebeca Lozano MD[3,4] | Roman Gulati MS[5] | Elisa M. Ledet PhD[6] | Navonil De Sarkar PhD[5] | Petros Grivas MD, PhD[5,7] | Celestia S. Higano MD[5,7] | Bruce Montgomery MD[7] | Peter S. Nelson MD[5,7] | David Olmos MD, PhD[3,4] | Vadim Sokolov PhD[6] | Michael T. Schweizer MD[5,7] | Todd A. Yezefski MD[7] | Evan Y. Yu MD[5,7] | Channing J. Paller MD[2] | Oliver Sartor MD[8] | Elena Castro MD, PhD[3,4,9] | Emmanuel S. Antonarakis MD[2] | Heather H. Cheng MD, PhD[5,7]

[1]Division of Medical Oncology, Oregon Health Science University, Portland, Oregon, USA

[2]Division on Medical Oncology, Johns Hopkins School of Medicine, Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland, USA

[3]Prostate Cancer Clinical Research Unit, Division on Medical Oncology, Spanish National Cancer Research Centre (CNIO), Madrid, Spain

[4]Division on Medical Oncology, Genitourinary Cancer Traslational Research Group, Instituto de Investigación Biomédica de Málaga, Malaga, Spain

[5]Fred Hutchinson Cancer Research Center, Seattle, Washington, USA

[6]Systems Engineering and Operations Research Department, George Mason University, Fairfax, Virginia, USA

[7]Division of Medical Oncology, Department of Medicine, University of Washington, Seattle, Washington, USA

[8]Division on Medical Oncology, Tulane University School of Medicine, New Orleans, Louisiana, USA

[9]Division on Medical Oncology, Hospital Universitario Virgen de la Victoria y Regional de Málaga, Málaga, Spain

Correspondence
Heather H. Cheng, MD, PhD, 1144 Eastlake Ave E, Seattle, WA 98109-1023 USA.
Email: hhcheng@uw.edu

Abstract

Background: Among men with metastatic prostate cancer, about 10% have germline alterations in DNA damage response genes. Most studies have examined *BRCA2* alone or an aggregate of *BRCA1/2* and *ATM*. Emerging data suggest that *ATM* mutations may have distinct biology and warrant individual evaluation. The objective of this study is to determine whether response to prostate cancer systemic therapies differs between men with germline mutations in *ATM* (g*ATM*) and *BRCA2* (g*BRCA2*).

Methods: This is an international multicenter retrospective matched cohort study of men with prostate cancer harboring g*ATM* or g*BRCA2*. PSA_{50} response (≥50% decline in prostate-specific antigen) was compared using Fisher's exact test.

Results and Limitations: The study included 45 g*ATM* and 45 g*BRCA2* patients, matched on stage and year of germline testing. Patients with g*ATM* and g*BRCA2* had similar age, Gleason grade, and PSA at diagnosis. We did not observe differences in PSA_{50} responses to abiraterone, enzalutamide, or docetaxel in metastatic castration resistant prostate cancer between the two groups; however, 0/7 with g*ATM* and 12/14 with g*BRCA2* achieved PSA_{50} response to PARPi ($p < .001$). Median (95% confidence interval) overall survival from diagnosis to death was 10.9 years (9.5-not reached) versus 9.9 years (7.1-not reached, $p = .07$) for the g*ATM* and g*BRCA2* cohorts, respectively. Limitations include the retrospective design and lack of mutation zygosity data.

Conclusions: Conventional therapies can be effective in g*ATM* carriers and should be considered before PARPi, which shows limited efficacy in this group. Men with g*ATM* mutations warrant prioritization for novel treatment strategies.

Funding information
Center for Strategic Scientific Initiatives, National Cancer Institute; Prostate Cancer Foundation; Institute for Prostate Cancer Research; Washington State Medical Oncology Society; Advancing Cancer Treatment; Patrick Walsh Prostate Cancer Research Fund; NCI; DoD

KEYWORDS
abiraterone, *ATM*, *BRCA2*, docetaxel, enzalutamide, germline, homologous recombination deficiency, PARPi, platinum

1 | INTRODUCTION

Approximately 10% of men with metastatic prostate cancer have germline (inherited) DNA damage response (gDDR) gene alterations. *BRCA2* is a homologous recombination (HR) gene and is the most frequent pathogenic germline alteration in advanced prostate cancer (3%–5%), followed by *ATM* (1.6%–2%) and *BRCA1* (0.8%–1.3%).[1–3] Several studies have shown that germline *BRCA2* mutations (g*BRCA2*) are associated with poor prognosis and worse prostate cancer outcomes and/or increased genomic instability.[3–8]

Castro et al.,[6] reported that at diagnosis, patients with prostate cancer and g*BRCA1/2* mutations are more likely to have Gleason Grade Group ≥4 disease, T3/4 stage, nodal involvement, metastases, and shorter cancer-specific survival compared to noncarriers. The IMPACT study showed that g*BRCA2* mutation carriers have a higher incidence of prostate cancer and are more likely to be diagnosed at a younger age and have clinically significant disease compared to noncarriers, whereas no difference in age or tumor characteristics was detected between g*BRCA1*- and noncarriers.[5] Na et al.,[9] reported that the combined g*BRCA1/2* and germline *ATM* (g*ATM*) mutation rate was higher in lethal prostate cancer compared to localized disease. However, features of tumors and treatment responses linked to g*ATM* mutations as a separate cohort are not characterized.

g*ATM* mutation carriers have not been well-characterized despite *ATM* being the second most frequently observed DNA damage response gene alteration in metastatic prostate cancer. Several retrospective and prospective studies have reported that *ATM*-deficient prostate tumors may have attenuated response to poly-ADP-ribose polymerase inhibitors (PARPi) and platinum chemotherapy.[7,10–15] Preliminary results of the phase II TRITON2 study demonstrated radiographic response to PARPi rucaparib in 51% (50/98) of men with *BRCA1/2* and only 4% (2/49) of men with *ATM* mutations.[11,16] The US Food and Drug Administration (FDA) granted rucaparib an accelerated approval for men with metastatic castration resistant prostate cancer (mCRPC) and *BRCA1/2* mutations who were previously treated with docetaxel. In the phase III randomized PROfound study of the PARPi olaparib vs AR targeting agent, the primary endpoint of radiographic progression-free survival (rPFS) in men with mCRPC harboring mutations in *BRCA1/2* and/or *ATM* (cohort A) was met, and olaparib also received FDA approval. While the primary endpoint was met for cohort A, in a post hoc subgroup analysis of men whose prostate cancer harbored *ATM* alterations, olaparib did not significantly improve rPFS (median 5.4 months vs. 4.7 months for controls).[12] One potential explanation for the observed differences in clinical activity of PARPi in men with *BRCA2* versus *ATM* mutations may relate to the distinctive roles these proteins play in HR repair, with *ATM* acting as a sensor of DNA double strand break and *BRCA2* being a core effector of HR DNA repair.

Conventional systemic prostate cancer therapies, such as androgen receptor (AR) targeted or taxane agents, are not currently selected by biomarkers. These therapies have been reported to be effective in g*BRCA1/2* carriers with prostate cancer.[3,17] PROREPAIR-B, a prospective cohort study, compared response outcomes for mCRPC treatments among g*BRCA2* carriers and non-carriers and showed similar response rates.[3] Efficacy in patients with g*ATM*, as a distinct cohort, has not been evaluated. Given the uncertain response to HR-deficiency targeted treatments in these men, we sought to investigate whether these patients respond to conventional biomarker-agnostic therapies. We hypothesized that, compared to men carrying g*BRCA2*, those carrying g*ATM* would have a similar response to AR-targeted agents and docetaxel yet attenuated responses to platinum and PARPi therapies.

2 | METHODS

This is an international, retrospective, matched cohort study of Consecutive patients with prostate cancer who underwent clinical germline genetic testing between 2014 and 2019 at the University of Washington (UW), Johns Hopkins (JH) Hospital, CNIO-IBIMA Genitourinary Cancer Unit, or Tulane University Cancer Center. We selected patients who had g*ATM* or g*BRCA2* mutations identified with germline genetic testing panels (Ambry Color, Invitae, Myriad, or in-house germline genetic testing at CNIO, JH, and UW). Only alterations designated as pathogenic or likely pathogenic by the American College of Medical Genetics were included.[18] The g*BRCA2* cohort was chosen as a comparison group because it has the most characterized HR-deficient prostate cancer phenotype and established management guidelines. To facilitate comparisons, the g*BRCA2* cohort was individually matched (1:1) to the g*ATM* group by stage at diagnosis (metastatic vs. nonmetastatic), year of germline testing and by center at which patients were treated.

A total of 45 patients with g*ATM* and 45 matched g*BRCA2* cases were included. Two patients included in the current study were also

reported in the analysis by Marshall et al.[10]: one g*ATM* and one g*BRCA2* mutation carrier. Medical records review was performed after local institutional review board approvals at participating centers.

2.1 | Statistical analysis

Baseline characteristics for g*ATM* and g*BRCA2* cohorts were compared using the Mann–Whitney test for continuous variables and Fisher's exact test for categorical variables. The primary efficacy endpoint was the percentage of men achieving at least one prostate-specific antigen value that was ≥50% below baseline (PSA_{50} response). Treatment-specific PSA_{50} responses were compared using Fisher's exact tests. Follow-up was calculated using reverse Kaplan-Meier estimation. Metastasis-free survival (MFS) was defined as time from diagnosis to death, last clinical evaluation, or evidence of metastasis on conventional imaging, determined at the local radiologists' discretion and broadly consistent with the Prostate Cancer Clinical Trials Working Group 3 guidelines.[19] Overall survival (OS) was defined as time from prostate cancer diagnosis to death or last clinical evaluation. Time on therapy was defined as time from initiation to termination of therapy or last clinical evaluation, and time to next treatment was defined as time from the start of treatment to the initiation of the next regimen or last clinical evaluation. OS, MFS, median time on therapy, and median time to next treatment were estimated using Kaplan–Meier methods. Differences between g*ATM* and g*BRCA2* cohorts were estimated using the log-rank test. All tests were two-sided and $p < .05$ was considered statistically significant. R, version 3.6.3, was used for statistical analysis.

3 | RESULTS

3.1 | Cohort characteristics

The study included 90 men with prostate cancer: 45 with g*ATM* mutations and 45 with g*BRCA2* mutations. Specific mutations in g*ATM* and g*BRCA2* genes are documented in Figure 1. Baseline characteristics, including age, PSA, Gleason Grade Group, were similar in the g*ATM* and g*BRCA2* cohorts (Table 1). A similar number of patients had a family history of cancer, meeting Prostate Cancer NCCN Guidelines[20] for germline testing. Distribution of pathology patterns (e.g., cribriform, neuroendocrine), definitive treatment, and anatomical sites of metastases were also similar between the two cohorts. The median follow-up time since diagnosis was 11.8 years in the g*ATM* cohort and 8.0 years in the g*BRCA2* cohort. Metastases developed in 23/28 g*ATM* and 20/28 g*BRCA2* patients after a median follow-up of 15.7 and 15.0 years, respectively, for the subgroup of men diagnosed with localized prostate cancer. Of the 12 men in the g*ATM* cohort and 14 men in the g*BRCA2* cohort for whom tumor sequencing results were available, none were reported to have somatic alterations in other HR genes.

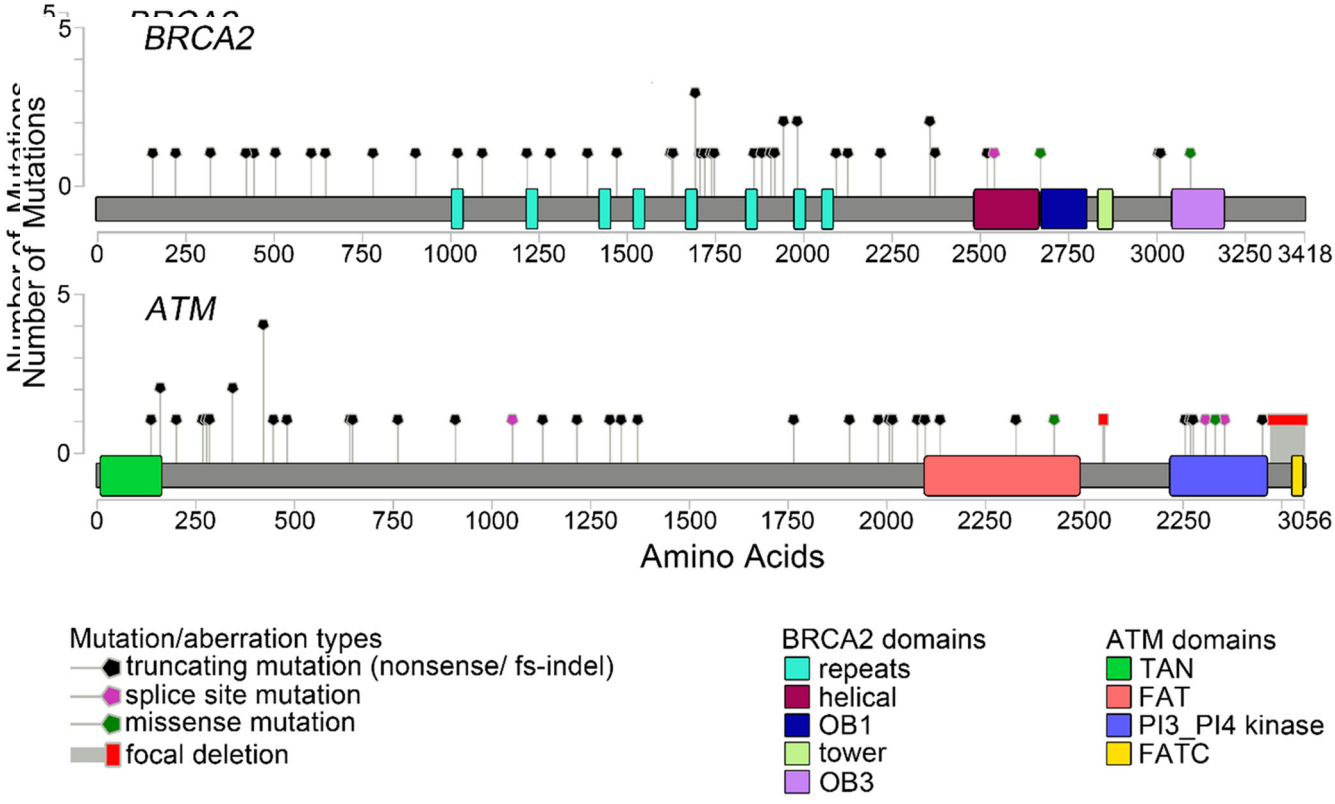


FIGURE 1 Distribution of *ATM* and *BRCA2* mutations [Color figure can be viewed at wileyonlinelibrary.com]

3.2 | PSA_{50} response rates

Responses to systemic therapies in the mCRPC setting, as measured by PSA_{50}, are summarized in Table 2. Comparing patients with g*ATM* versus g*BRCA2* mutations, there was no evident difference in PSA_{50} response to abiraterone: 9/16 (56%) versus 11/19 (58%); to enzalutamide: 9/16 (56%) versus 8/12 (67%); or to docetaxel: 9/13 (69%) versus 9/16 (60%). Only 1 of 3 patients with g*ATM* versus 5 of 7 patients with g*BRCA2* responded to platinum, numbers are too small to draw conclusions. In contrast, there appeared to be a difference in responses to PARPi—0/7 (0%) patients with g*ATM* mutations responded versus 12/14 (86%) patients with g*BRCA2* mutations ($p < .001$).

TABLE 1 Patient characteristics

Characteristics	g*ATM*	g*BRCA2*	*p*
Number of patients	45	45	
Stage M1 at diagnosis (%)	17 (38)	17 (38)	
Age (median [IQR])	58 [54, 66]	62 [55, 67]	.2
PSA (median [IQR])	24 [9, 76]	11 [6, 46]	.13
Grade (%)			
2	6 (17)	4 (11)	
3	7 (20)	5 (14)	
4	5 (14)	8 (22)	
5	17 (49)	20 (54)	
Family history of cancer meeting Prostate Cancer NCCN Guidelines for germline testing[20] (%)	25 (60)	29 (71)	.4
Known other primary cancers (%)	5 (11)	4 (9)	>.9
Pathology (%)			
acinar	24 (80)	22 (76)	
ductal	3 (10)	3 (10)	
intraductal	0 (0)	1 (3)	
cribriform	1 (3)	1 (3)	
neuroendocrine	2 (7)	2 (7)	
Prostatectomy (%)	20 (44)	22 (50)	.7
Radiotherapy (%)	22 (51)	24 (56)	.8
Bone metastasis at the time of diagnosis (%)	14 (31)	15 (33)	>.9
Nodal metastasis at the time of diagnosis (%)	13 (29)	11 (24)	.8
Visceral metastasis at the time of diagnosis (%)	1 (2)	3 (7)	.6

3.3 | Time on treatment

Median time on mCRPC treatment for the g*ATM* and g*BRCA2* cohorts is shown in Table 3. Overall, for abiraterone, enzalutamide, and docetaxel, there was no evidence of different duration from the start to the end of treatment between the cohorts. In the mCRPC setting, median (95% confidence interval [CI]) time on AR-targeted therapies in g*ATM* compared to g*BRCA2* cohort was 9.7 (6.5–23) versus 6.4 (5.4–15.5) months for abiraterone ($p = .5$); 6.5 (4.6-not reached) vs 9 (4.9-not reached) months for enzalutamide ($p > .9$); and 5.1 (3.7-not reached) versus 4 (3–6) months for docetaxel-based chemotherapy ($p = .06$). Median time on platinum-based chemotherapy in the mCRPC setting was 3 (1-not reached) months in the g*ATM* cohort compared to 6 (4-not reached) months in the g*BRCA2* cohort ($p = .11$). We observed a difference in treatment duration on PARPi: 3 (2-not reached) months in the g*ATM* cohort compared to 12 (6.9-not reached) months in the g*BRCA2* cohort ($p = .004$). Time on treatment for each therapy is shown in Figures 5SA–SE.

3.4 | Overall survival

During the study follow-up period, 15/45 (33.3%) g*ATM* and 18/45 (40%) g*BRCA2* patients died. Median (95% CI) OS from diagnosis to death was 10.9 years (9.5-not reached) versus 9.9 years (7.1-not reached, $p = .07$) for the g*ATM* and g*BRCA2* cohorts, respectively (Figure 2). There was no evidence of OS difference between g*ATM* and g*BRCA2* cohorts when analyzing subgroups of patients initially diagnosed with localized (not reached vs 9.9 years, respectively, $p = .07$) or metastatic disease (8.7 vs. 3.6 years, respectively, $p = .4$; Figure S3).

TABLE 2 PSA_{50} response

Therapy	Prior	g*ATM*	g*BRCA2*	*p*
Abiraterone	Overall	9/16 (56%)	11/19 (58%)	>.9
	Pre-enza	9/14 (64%)	10/17 (59%)	
	Post-enza	0/2 (0%)	1/2 (50%)	
Enzalutamide	Overall	9/16 (56%)	8/12 (67%)	.7
	Pre-abi	7/10 (70%)	5/7 (71%)	
	Post-abi	2/6 (33%)	3/5 (60%)	
Docetaxel	Overall	9/13 (69%)	9/16 (56%)	.7
	Pre-abi/enza	7/9 (78%)	4/7 (57%)	
	Post-abi/enza	2/4 (50%)	5/9 (56%)	
PARPi	Overall	0/7 (0%)	12/14 (86%)	<.001
	Pre-plat	0/3 (0%)	10/11 (91%)	
	Post-plat	0/4 (0%)	2/3 (67%)	

TABLE 3 Time on treatment

Therapy	Setting	*gATM* Number of pts	*gATM* Median time on therapy (95% CI)	*gBRCA2* Number of pts	*gBRCA2* Median time on therapy (95% CI)	*P*
Abiraterone	Overall	19	9.71 (6.5–23)	24	6.44 (5–15.5)	.6
	HSPC	2	3 (3-N/A)	5	6 (5-N/A)	>.9
	CRPC	17	9.71 (6.5–23)	19	6.44 (5.38–15.5)	.5
Enzalutamide	CRPC	16	6.5 (4.62-N/A)	12	9 (4.92-N/A)	>.9
PARPi	CRPC	7	3 (2-N/A)	15	12 (6.9-N/A)	.004
Platinum	CRPC	3	3 (1-N/A)	7	6 (4-N/A)	.11
Docetaxel	Overall	18	4.13 (4–7)	21	4 (3–6)	.12
	HSPC	5	4 (N/A-N/A)	4	4.5 (3-N/A)	.4
	CRPC	13	5.12 (3.7-N/A)	17	4 (3–6)	.06
			Median time to next therapy (CI 95%)		Median time to next therapy (CI 95%)	
	CRPC	13	10.47 (6.47-N/A)	15	7 (4.16–12.82)	.15

Abbreviations: CRPC, castration resistant prostate cancer; HSPC, hormone sensitive prostate cancer; Pts, patients.

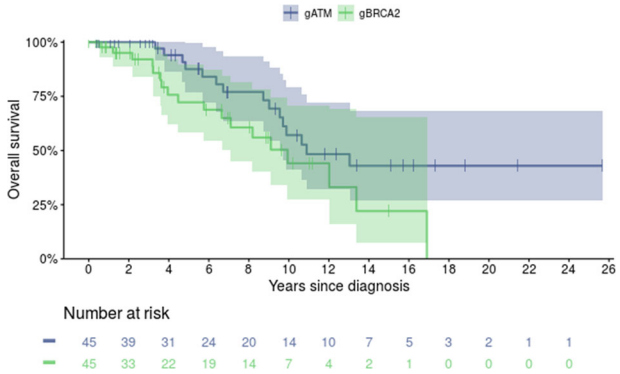


FIGURE 2 Overall survival [Color figure can be viewed at wileyonlinelibrary.com]

Among the 28 patients in each cohort diagnosed with localized prostate cancer, median (95% CI) MFS was 5.7 years (5.1–11.1) versus 5.0 years (4.1–7.0, $p = .13$) for the g*ATM* and g*BRCA2* cohorts, respectively (Figure S4).

4 | DISCUSSION

Prostate tumors with alterations in DDR genes, particularly those in the HR repair pathway, represent a group of interest particularly in light of recent FDA approvals of the PARP inhibitors rucaparib and olaparib. While broadly grouped with g*BRCA1/2* carriers, patients with prostate cancer in the setting of g*ATM* mutations have not been characterized as an independent cohort. This study focuses on patients with prostate cancer and g*ATM* mutations and describes responses to conventional and emerging systemic therapies with the aim of improving our understanding of therapeutic approaches for these patients.

Among men diagnosed with prostate cancer, those carrying g*BRCA2* mutations are recognized to have a more aggressive phenotype (Table S3).[6] Another retrospective study, albeit with limited numbers of g*ATM* carriers, found that g*BRCA1/2* and g*ATM* are associated with earlier age of death and shorter cancer-specific survival.[9] Dedicated attention is warranted for g*ATM* mutation carriers to further define specific prostate cancer risks and response to treatment.

Our data support the concept that while *ATM*-deficient prostate cancer may share features with *BRCA2*-deficient tumors, such as enrichment in the metastatic setting and response to nontargeted agents, they have distinct clinical characteristics. For example, we observed an attenuated response to PARPi in the g*ATM* cohort compared to the g*BRCA2* cohort, consistent with a retrospective study by Marshall et al.,[10] in which 0/8 patients with germline or somatic *ATM* mutations responded to PARPi. This difference in sensitivity to PARPi may partially be explained by different roles for *ATM* and *BRCA2* in the HR repair pathway. ATM's primary role is to recognize double-strand break and to activate downstream HR repair proteins, such as Chk2.[21–23] Once activated, Chk2 has an overlapping function with ATM and phosphorylates the core HR repair pathway effectors, for example, BRCA1, BRCA2.[21] Chk2 can be activated by proteins other than ATM, such as DNA-dependent protein kinase, suggesting that HR repair pathway can be activated even in cells with loss of ATM function.[22] These mechanistic differences in *ATM* and *BRCA2* may account for observed differences in sensitivity to HR-targeted therapies between the two cohorts of our study. In addition, Neeb et al.,[7] have recently reported that ATM protein

expression as measured by ATM IHC is not perfectly overlapping with *ATM* mutations identified by NGS and suggest that protein expression may be another factor for treatment selection, potentially more predictive than DNA sequencing.

Abiraterone, enzalutamide, and docetaxel have mechanisms of action largely independent of *BRCA2* and *ATM*. A previous study reported that these therapies are similarly effective in g*BRCA2* mutation carriers compared to noncarriers and g*BRCA2* mutation carriers might benefit from upfront androgen-directed therapy rather than taxanes.[3] We observed comparable PSA_{50} response rates in the two cohorts in our study. Thus, our data suggest that abiraterone, enzalutamide, and docetaxel should be offered to patients with mCRPC who carry g*ATM* mutations.

Recent data suggest that platinum chemotherapy is effective in patients with *BRCA2* mutations.[24–26] In our study, patients with g*ATM* mutations appeared to have a reduced response to platinum chemotherapy compared to the g*BRCA2* cohort, but this comparison was not statistically significant owing to the small numbers. However, our observations are consistent with other studies reporting disappointing responses to platinum chemotherapy among *ATM* mutation carriers with prostate cancer.[15,26] To date, reported numbers of patients with mCRPC and *ATM* alterations treated with platinum chemotherapy remain small and further studies are needed.

Our data highlight the need to explore new targeted therapies in patients with mCRPC and *ATM* alterations. Preclinical data suggest that *ATM*-deficient prostate tumors may be sensitive to *ATR* inhibitors, which, when combined with PARPi, result in apoptosis in PARPi-resistant prostate cancer cell lines.[7,27] Several ongoing clinical trials are evaluating *ATR* inhibitors in prostate cancer (e.g., NCT04267939, NCT03787680).

We did not observe a significant difference in OS between the two cohorts, although this could be attributable to the limited numbers of patients and deaths and to different proportions of men receiving PARPi in the two groups. More men in g*BRCA2* cohort received PARPi, which has a proven OS benefit for these patients.[12,28]

There are a number of important limitations to our study. First, this is a non-randomized retrospective study with a relatively small sample size. Second, the indications for germline testing in prostate cancer have been and remain evolving, so there are likely differences in practice from 2014 to 2019, as well as ascertainment biases. We attempted to minimize confounding effect by matching cases by year of testing; we acknowledge that men undergoing germline testing 2014–2019 will have been largely those with a strong family history of cancer and/or aggressive phenotype, although both g*ATM* and g*BRCA2* cohorts are likely to have been similarly affected. Third, the two cohorts are matched only for the year of testing, stage at diagnosis and treatment center; other patient characteristics were not matched. Fourth, the study does not include a control group of men without g*ATM* and g*BRCA2* mutations, which limits broader implications for treatment response. Fifth, the study does not include radiographic response assessment or confirmed PSA_{50} responses, limiting treatment response assessments. Clinical practices at different institutions may vary. For example, imaging was performed at clinician discretion without predefined standard intervals, which may have affected the time on treatment and MFS assessments. Finally, somatic alterations in other genes, mutation zygosity and protein expression were not fully addressed, but interference from clonal hematopoiesis of indeterminant potential would be less of an issue.[29] Nevertheless, given the greater prevalence of g*ATM* mutations[30,31] in general population, compared to g*BRCA2* mutations,[32,33] we believe that specific examination of g*ATM* remains important to this patient population.

5 | CONCLUSIONS

Our data provide evidence that standard therapies may be similarly effective in g*ATM*- and g*BRCA2*-associated prostate cancer, whereas PARPi appear less effective in g*ATM*-associated prostate cancer. We did not find that abiraterone, enzalutamide, and docetaxel were less effective in patients with prostate cancer with g*ATM* mutations and thus these agents should remain standard of care options for patients. This important subgroup of patients should continue to be studied and incorporated into clinical trials—especially those incorporating novel agents and combination strategies, for example, ATR inhibitors.

ACKNOWLEDGEMENTS

We thank Agnes Gawne for data collection assistance. We gratefully acknowledge funding support from the Institute for Prostate Cancer Research, Prostate Cancer Foundation, Washington State Medical Oncology Society, Advancing Cancer Treatment, Patrick Walsh Prostate Cancer Research Fund, and NCI award numbers CA097186 (Pacific Northwest Prostate Cancer SPORE), P30 CA015704, P30 CA006973-52, R01 CA238384, R50 CA221836, and T32CA009515; PCF YI VALor award, CDMRP Awards W81XWH-17-2-0043, W81XWH-15-1-0430, PC170503, PC171001, DOD EIRA award W81XWH-17-1-0380 and the DOD Clinical Consortium award W81XWH-16-PCRP-CCRSA.

CONFLICT OF INTERESTS

Catherine H. Marshall: Consulting from Dendreon, Bayer, McGraw-Hill Publishing Company. Travel from Dava Oncology.

Rebeca Lozano: speaker fees from Roche, Janssen, Sanofi and Bayer. Travel support from Roche, Janssen, Sanofi and Astellas Pharma.

Petros Grivas: received grants from Bavarian Nordic, Bristol Myers Squibb, Clovis Oncology, Debiopharm, EMD Serono, GlaxoSmithKline, Immunomedics, Kure It Cancer Research, Merck & Co., Mirati Therapeutics, Pfizer, QED Therapeutics. Dr. Grivas has received consulting fees from AstraZeneca, Astellas Pharma, Bayer, Bristol Myers Squibb, Clovis Oncology, Dyania Health, Driver, EMD Serono, Exelixis, Foundation Medicine, Genentech/Roche, Genzyme, GlaxoSmithKline, Guardant Health, Heron Therapeutics, Immunomedics/Gilead, Infinity Pharmaceuticals, Janssen, Merck &

Co., Mirati Therapeutics, Pfizer, QED Therapeutics, Regeneron Pharmaceuticals, Seattle Genetics, 4D Pharma PLC.Celestia S. Higano: Institutional research funding: Aptevo, Aragon, Astellas, AstraZeneca, Clovis, Dendreon, eFFECTOR Therapeutics, Emergent, Ferring, Genentech, Hoffman-La roche, Medivation, Pfizer; Consulting, scientific advisory boards: Astellas, Bayer, Blue Earth Diagnositics, Clovis, Dendreon, Ferring, Hinova, Janssen, Merck, Orion, Pfizer, Tolmar, Carrick Therapeutics, Novartis, Genentech; Other: spouse holds stock and former officer of CTI Biopharma.

Bruce Montgomery: Institutional research funding: Astellas, AstraZeneca, Beigene, Clovis, Janssen.

Peter S. Nelson: Consultant for Bristol Myers Squibb, Astellas, and Janssen Pharmaceuticals and received fees from UpToDate.

David Olmos: grant research support (to the institution) from AstraZeneca, Astellas, Bayer, Jansen. Advisory board and speaker fees from AstraZeneca, Astellas, Bayer, BioOncotech (Uncompensated), Clovis, Daiichi-Sankyo, Jansen, MSD, Pfizer. Travel support from AstraZeneca, Astellas, Bayer, F. Hoffman La Roche, Genetech, Ipsen, Jansen.

Michael T. Schweizer: Paid consultant for Janssen and Resverlogix. Research funding from Bristol Myers Squibb, Merck, Immunomedics, Janssen, AstraZeneca, Pfizer, Madison Vaccines, Tmunity and Hoffman-La Roche.

Todd A. Yezefski: consultant for Dendreon.

Evan Y. Yu: Consulting—Advanced Accelerator Applications, Bayer, Clovis, Janssen, Merck. Research to institution—Bayer, Blue Earth, Dendreon, Merck, Taiho.

Oliver Sartor: Grant support to institution for AAA Pharma, AstraZeneca, Bayer, Endocyte, Progenics, Novartis, and Janssen, consulting fees from Astellas, Blue Earth Diagnostics, EMD Serono, Pfizer, Constellation, Dendreon, Bristol-Myers Squibb, Invitae, Merck, Innocrin, and Sotio, Consulting fees from AAA Pharma, AstraZeneca, Bayer, Endocyte, Progenics, Novartis, Janssen, Astellas, Blue Earth Diagnostics, EMD Serono, Pfizer, Constellation, Noria Therapeutics, Clovis, Myriad, Noxopharm, Point Biopharm, Tenebio, Theragnostics, Telix, Clarity Pharmaceuticals, and Fusion.

Elena Castro: honoraria and consulting CLOVIS, AstraZeneca, Astellas, Jansen, MSD, Roche, Pfizer; research funding AstraZeneca, Bayer, Janssen, travel accommodations AstraZeneca, Bayer, Janssen.

Emmanuel S. Antonarakis: has served as a paid consultant/advisor for Invitae, Janssen, Pfizer, Sanofi, Dendreon, Merck, Bristol-Myers Squibb, AstraZeneca, Clovis, Bayer, Constellation, Eli Lilly and Amgen; and has received research funding to his institution from Janssen, Johnson & Johnson, Sanofi, Dendreon, Genentech, Novartis, Bayer, Merck, Bristol-Myers Squibb, AstraZeneca, ESSA and Constellation.

Heather H. Cheng; Research funding to institution from Clovis, Janssen, Sanofi, Medivation/Astellas, Color Foundation; Consultancy to AstraZeneca; Royalties from up to date. The other authors declare that there are no conflict of interests.

ETHICS STATEMENT

This study was approved by IRB board at each participating site.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

ORCID

Alexandra O. Sokolova http://orcid.org/0000-0003-0821-6503
Roman Gulati http://orcid.org/0000-0002-7592-6567
Elisa M. Ledet http://orcid.org/0000-0003-1230-3255
Michael T. Schweizer http://orcid.org/0000-0002-5510-0661
Channing J. Paller http://orcid.org/0000-0003-3658-1858
Oliver Sartor http://orcid.org/0000-0002-8777-7343
Emmanuel S. Antonarakis http://orcid.org/0000-0003-0031-9655
Heather H. Cheng http://orcid.org/0000-0002-1365-0702

REFERENCES

1. Pritchard CC, Mateo J, Walsh MF, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. *N Engl J Med*. 2016;375:443-453.
2. Nicolosi P, Ledet E, Yang S, et al. Prevalence of germline variants in prostate cancer and implications for current genetic testing guidelines. *JAMA Oncol*. 2019;5:523-528.
3. Castro E, Romero-Laorden N, Del Pozo A, et al. PROREPAIR-B: a prospective cohort study of the impact of germline DNA repair mutations on the outcomes of patients with metastatic castration-resistant prostate cancer. *J Clin Oncol*. 2019;37:490-503.
4. Cheng HH, Sokolova AO, Schaeffer EM, Small EJ, Higano CS. Germline and somatic mutations in prostate cancer for the clinician. *J Natl Compr Canc Netw*. 2019;17:515-521.
5. Page EC, Bancroft EK, Brook MN, et al. Interim results from the IMPACT Study: evidence for prostate-specific antigen screening in BRCA2 mutation carriers. *Eur Urol*. 2019;76:831-842.
6. Castro E, Goh C, Olmos D, et al. Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. *J Clin Oncol*. 2013;31:1748-1757.
7. Neeb A, Herranz N, Arce-Gallego S, et al. Advanced prostate cancer with ATM loss: PARP and ATR inhibitors. *Eur Urol*. 2020;0:200-211.
8. Carter HB, Helfand B, Mamawala M, et al. Germline mutations in ATM and BRCA1/2 are associated with grade reclassification in men on active surveillance for prostate cancer. *Eur Urol*. 2018;75:743-749. https://doi.org/10.1016/j.eururo.2018.09.021
9. Na R, Zheng SL, Han M, et al. Germline mutations in ATM and BRCA1/2 distinguish risk for lethal and indolent prostate cancer and are associated with early age at death. *Eur Urol*. 2017;71:740-747.
10. Marshall CH, Sokolova AO, McNatty AL, et al. Differential response to olaparib treatment among men with metastatic castration-resistant prostate cancer harboring BRCA1 or BRCA2 Versus ATM mutations. *Eur Urol*. 2019;76:452-458.
11. Abida W, Patnaik A, Campbell D, et al. Rucaparib in men with metastatic castration-resistant prostate cancer harboring a BRCA1 or BRCA2 Gene Alteration. *J Clin Oncol*. 2020;20:01035-03772. https://doi.org/10.1200/JCO.20.01035
12. De Bono J, Mateo J, Fizazi K, et al. Olaparib for metastatic castration-resistant prostate cancer. *N Engl J Med*. 2020;382:2091-2102.
13. Sokolova AO, Yu EY, Cheng HH. Honing in on PARPi response in prostate cancer: from HR pathway to gene-by-gene granularity. *Clin Cancer Res*. 2020;26:2439-2440.
14. Athie A, Arce-Gallego S, Gonzalez M, et al. Targeting DNA repair defects for precision medicine in prostate cancer. *Curr Oncol Rep*. 2019;21:42.
15. Mota JM, Barnett E, Nauseef JT, et al. Platinum-based chemotherapy in metastatic prostate cancer with DNA repair gene alterations. *JCO Precis Oncol*. 2020;4:355-366. https://doi.org/10.1200/PO.19.00346

16. Abida W, Campbell D, Patnaik A, et al. Non-BRCA DNA damage repair gene alterations and response to the PARP inhibitor rucaparib in metastatic castration-resistant prostate cancer: analysis from the phase II TRITON2 Study. *Clin Cancer Res*. 2020;26:2487-2496.
17. Carlson AS, Acevedo RI, Lim DM, et al. Impact of mutations in homologous recombination repair genes on treatment outcomes for metastatic castration resistant prostate cancer. *PLoS One*. 2020;15:0239686.
18. Karbassi I, Maston GA, Love A, et al. A standardized DNA variant scoring system for pathogenicity assessments in mendelian disorders. *Hum Mutat*. 2016;37:127-134.
19. Scher HI, Morris MJ, Stadler WM, et al. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the prostate cancer clinical trials working group 3. *J Clin Oncol*. 2016;34:1402-1418.
20. National Comprehensive Cancer Network. Prostate Cancer (Version 2.2020). https://www.nccn.org/professionals/physician_gls/pdf/prostate_blocks.pdf. Accessed November 10, 2020.
21. Zannini L, Delia D, Buscemi G. CHK2 kinase in the DNA damage response and beyond. *J Mol Cell Biol*. 2014;6:442-457.
22. Li J, Stern DF. Regulation of CHK2 by DNA-dependent protein kinase. *J Biol Chem*. 2005;280:12041-12050.
23. Lavin MF, Delia D, Chessa L. ATM and the DNA damage response. Workshop on ataxia-telangiectasia and related syndromes. *EMBO Rep*. 2006;7:154-160.
24. Pomerantz MM, Spisák S, Jia L, et al. The association between germline BRCA2 variants and sensitivity to platinum-based chemotherapy among men with metastatic prostate cancer. *Cancer*. 2017;123:3532-3539.
25. Cheng HH, Pritchard CC, Boyd T, Nelson PS, Montgomery B. Biallelic inactivation of BRCA2 in platinum sensitive, metastatic castration resistant prostate cancer. *Eur Urol*. 2016;69:992-995.
26. Schmid S, Omlin A, Higano C, et al. Activity of platinum-based chemotherapy in patients with advanced prostate cancer with and without DNA repair gene aberrations. *JAMA Netw. Open*. 2020;3:e2021692.
27. Rafiei S, Fitzpatrick K, Liu D, et al. ATM loss confers greater sensitivity to ATR inhibition than PARP inhibition in prostate cancer. *Cancer Res*. 2020;80:2094-2100.
28. Hussain M, Mateo J, Fizazi K, et al. Survival with olaparib in metastatic castration-resistant. *N Engl J Med*. 2020;383:2345-2357.
29. Sokolova AO, Shirts BH, Konnick EQ, et al. Complexities of next-generation sequencing in solid tumors: case studies. *J Natl Compr Canc Netw*. 2020;18:1150-1155.
30. Broeks A, Urbanus JH, Floore AN, et al. ATM-heterozygous germline mutations contribute to breast cancer–susceptibility. *Am J Hum Genet*. 2000;66:494-500.
31. Hall MJ, Bernhisel R, Hughes E, et al. Germline pathogenic variants in the ataxia telangiectasia mutated (ATM) gene are associated with high and moderate risks for multiple. *Cancers. Cancer Prev Res (Phila. Pa)*. 2021;14:433-440.
32. Maxwell KN, Domchek SM, Nathanson KL, Robson ME. Population frequency of germline BRCA1/2 mutations. *J Clin Oncol*. 2016;34:4183-4185.
33. Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. Br. J. Cancer 83, 1301–1308 (2000).

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Sokolova AO, Marshall CH, Lozano R, et al. Efficacy of systemic therapies in men with metastatic castration resistant prostate cancer harboring germline *ATM* versus *BRCA2* mutations. *The Prostate*. 2021;1-8. https://doi.org/10.1002/pros.24236

Received: 24 June 2021 | Accepted: 30 August 2021

DOI: 10.1002/pros.24236

ORIGINAL ARTICLE

The Prostate WILEY

Efficacy of systemic therapies in men with metastatic castration resistant prostate cancer harboring germline *ATM* versus *BRCA2* mutations

Alexandra O. Sokolova MD[1] | Catherine H. Marshall MD, MPH[2] | Rebeca Lozano MD[3,4] | Roman Gulati MS[5] | Elisa M. Ledet PhD[6] | Navonil De Sarkar PhD[5] | Petros Grivas MD, PhD[5,7] | Celestia S. Higano MD[5,7] | Bruce Montgomery MD[7] | Peter S. Nelson MD[5,7] | David Olmos MD, PhD[3,4] | Vadim Sokolov PhD[6] | Michael T. Schweizer MD[5,7] | Todd A. Yezefski MD[7] | Evan Y. Yu MD[5,7] | Channing J. Paller MD[2] | Oliver Sartor MD[8] | Elena Castro MD, PhD[3,4,9] | Emmanuel S. Antonarakis MD[2] | Heather H. Cheng MD, PhD[5,7]

[1]Division of Medical Oncology, Oregon Health Science University, Portland, Oregon, USA

[2]Division on Medical Oncology, Johns Hopkins School of Medicine, Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland, USA

[3]Prostate Cancer Clinical Research Unit, Division on Medical Oncology, Spanish National Cancer Research Centre (CNIO), Madrid, Spain

[4]Division on Medical Oncology, Genitourinary Cancer Traslational Research Group, Instituto de Investigación Biomédica de Málaga, Malaga, Spain

[5]Fred Hutchinson Cancer Research Center, Seattle, Washington, USA

[6]Systems Engineering and Operations Research Department, George Mason University, Fairfax, Virginia, USA

[7]Division of Medical Oncology, Department of Medicine, University of Washington, Seattle, Washington, USA

[8]Division on Medical Oncology, Tulane University School of Medicine, New Orleans, Louisiana, USA

[9]Division on Medical Oncology, Hospital Universitario Virgen de la Victoria y Regional de Málaga, Málaga, Spain

Correspondence
Heather H. Cheng, MD, PhD, 1144 Eastlake Ave E, Seattle, WA 98109-1023 USA.
Email: hhcheng@uw.edu

Abstract

Background: Among men with metastatic prostate cancer, about 10% have germline alterations in DNA damage response genes. Most studies have examined *BRCA2* alone or an aggregate of *BRCA1/2* and *ATM*. Emerging data suggest that *ATM* mutations may have distinct biology and warrant individual evaluation. The objective of this study is to determine whether response to prostate cancer systemic therapies differs between men with germline mutations in *ATM* (g*ATM*) and *BRCA2* (g*BRCA2*).

Methods: This is an international multicenter retrospective matched cohort study of men with prostate cancer harboring g*ATM* or g*BRCA2*. PSA_{50} response (≥50% decline in prostate-specific antigen) was compared using Fisher's exact test.

Results and Limitations: The study included 45 g*ATM* and 45 g*BRCA2* patients, matched on stage and year of germline testing. Patients with g*ATM* and g*BRCA2* had similar age, Gleason grade, and PSA at diagnosis. We did not observe differences in PSA_{50} responses to abiraterone, enzalutamide, or docetaxel in metastatic castration resistant prostate cancer between the two groups; however, 0/7 with g*ATM* and 12/14 with g*BRCA2* achieved PSA_{50} response to PARPi ($p < .001$). Median (95% confidence interval) overall survival from diagnosis to death was 10.9 years (9.5-not reached) versus 9.9 years (7.1-not reached, $p = .07$) for the g*ATM* and g*BRCA2* cohorts, respectively. Limitations include the retrospective design and lack of mutation zygosity data.

Conclusions: Conventional therapies can be effective in g*ATM* carriers and should be considered before PARPi, which shows limited efficacy in this group. Men with g*ATM* mutations warrant prioritization for novel treatment strategies.

Funding information

Center for Strategic Scientific Initiatives, National Cancer Institute; Prostate Cancer Foundation; Institute for Prostate Cancer Research; Washington State Medical Oncology Society; Advancing Cancer Treatment; Patrick Walsh Prostate Cancer Research Fund; NCI; DoD

KEYWORDS

abiraterone, *ATM*, *BRCA2*, docetaxel, enzalutamide, germline, homologous recombination deficiency, PARPi, platinum

1 | INTRODUCTION

Approximately 10% of men with metastatic prostate cancer have germline (inherited) DNA damage response (gDDR) gene alterations. *BRCA2* is a homologous recombination (HR) gene and is the most frequent pathogenic germline alteration in advanced prostate cancer (3%–5%), followed by *ATM* (1.6%–2%) and *BRCA1* (0.8%–1.3%).[1–3] Several studies have shown that germline *BRCA2* mutations (g*BRCA2*) are associated with poor prognosis and worse prostate cancer outcomes and/or increased genomic instability.[3–8]

Castro et al.,[6] reported that at diagnosis, patients with prostate cancer and g*BRCA1/2* mutations are more likely to have Gleason Grade Group ≥4 disease, T3/4 stage, nodal involvement, metastases, and shorter cancer-specific survival compared to noncarriers. The IMPACT study showed that g*BRCA2* mutation carriers have a higher incidence of prostate cancer and are more likely to be diagnosed at a younger age and have clinically significant disease compared to noncarriers, whereas no difference in age or tumor characteristics was detected between g*BRCA1*- and noncarriers.[5] Na et al.,[9] reported that the combined g*BRCA1/2* and germline *ATM* (g*ATM*) mutation rate was higher in lethal prostate cancer compared to localized disease. However, features of tumors and treatment responses linked to g*ATM* mutations as a separate cohort are not characterized.

g*ATM* mutation carriers have not been well-characterized despite *ATM* being the second most frequently observed DNA damage response gene alteration in metastatic prostate cancer. Several retrospective and prospective studies have reported that *ATM*-deficient prostate tumors may have attenuated response to poly-ADP-ribose polymerase inhibitors (PARPi) and platinum chemotherapy.[7,10–15] Preliminary results of the phase II TRITON2 study demonstrated radiographic response to PARPi rucaparib in 51% (50/98) of men with *BRCA1/2* and only 4% (2/49) of men with *ATM* mutations.[11,16] The US Food and Drug Administration (FDA) granted rucaparib an accelerated approval for men with metastatic castration resistant prostate cancer (mCRPC) and *BRCA1/2* mutations who were previously treated with docetaxel. In the phase III randomized PROfound study of the PARPi olaparib vs AR targeting agent, the primary endpoint of radiographic progression-free survival (rPFS) in men with mCRPC harboring mutations in *BRCA1/2* and/or *ATM* (cohort A) was met, and olaparib also received FDA approval. While the primary endpoint was met for cohort A, in a post hoc subgroup analysis of men whose prostate cancer harbored *ATM* alterations, olaparib did not significantly improve rPFS (median 5.4 months vs. 4.7 months for controls).[12] One potential explanation for the observed differences in clinical activity of PARPi in men with *BRCA2* versus *ATM* mutations may relate to the distinctive roles these proteins play in HR repair, with *ATM* acting as a sensor of DNA double strand break and *BRCA2* being a core effector of HR DNA repair.

Conventional systemic prostate cancer therapies, such as androgen receptor (AR) targeted or taxane agents, are not currently selected by biomarkers. These therapies have been reported to be effective in g*BRCA1/2* carriers with prostate cancer.[3,17] PROREPAIR-B, a prospective cohort study, compared response outcomes for mCRPC treatments among g*BRCA2* carriers and non-carriers and showed similar response rates.[3] Efficacy in patients with g*ATM*, as a distinct cohort, has not been evaluated. Given the uncertain response to HR-deficiency targeted treatments in these men, we sought to investigate whether these patients respond to conventional biomarker-agnostic therapies. We hypothesized that, compared to men carrying g*BRCA2*, those carrying g*ATM* would have a similar response to AR-targeted agents and docetaxel yet attenuated responses to platinum and PARPi therapies.

2 | METHODS

This is an international, retrospective, matched cohort study of Consecutive patients with prostate cancer who underwent clinical germline genetic testing between 2014 and 2019 at the University of Washington (UW), Johns Hopkins (JH) Hospital, CNIO-IBIMA Genitourinary Cancer Unit, or Tulane University Cancer Center. We selected patients who had g*ATM* or g*BRCA2* mutations identified with germline genetic testing panels (Ambry Color, Invitae, Myriad, or in-house germline genetic testing at CNIO, JH, and UW). Only alterations designated as pathogenic or likely pathogenic by the American College of Medical Genetics were included.[18] The g*BRCA2* cohort was chosen as a comparison group because it has the most characterized HR-deficient prostate cancer phenotype and established management guidelines. To facilitate comparisons, the g*BRCA2* cohort was individually matched (1:1) to the g*ATM* group by stage at diagnosis (metastatic vs. nonmetastatic), year of germline testing and by center at which patients were treated.

A total of 45 patients with g*ATM* and 45 matched g*BRCA2* cases were included. Two patients included in the current study were also

reported in the analysis by Marshall et al.[10]: one g*ATM* and one g*BRCA2* mutation carrier. Medical records review was performed after local institutional review board approvals at participating centers.

2.1 | Statistical analysis

Baseline characteristics for g*ATM* and g*BRCA2* cohorts were compared using the Mann–Whitney test for continuous variables and Fisher's exact test for categorical variables. The primary efficacy endpoint was the percentage of men achieving at least one prostate-specific antigen value that was ≥50% below baseline (PSA_{50} response). Treatment-specific PSA_{50} responses were compared using Fisher's exact tests. Follow-up was calculated using reverse Kaplan-Meier estimation. Metastasis-free survival (MFS) was defined as time from diagnosis to death, last clinical evaluation, or evidence of metastasis on conventional imaging, determined at the local radiologists' discretion and broadly consistent with the Prostate Cancer Clinical Trials Working Group 3 guidelines.[19] Overall survival (OS) was defined as time from prostate cancer diagnosis to death or last clinical evaluation. Time on therapy was defined as time from initiation to termination of therapy or last clinical evaluation, and time to next treatment was defined as time from the start of treatment to the initiation of the next regimen or last clinical evaluation. OS, MFS, median time on therapy, and median time to next treatment were estimated using Kaplan–Meier methods. Differences between g*ATM* and g*BRCA2* cohorts were estimated using the log-rank test. All tests were two-sided and $p < .05$ was considered statistically significant. R, version 3.6.3, was used for statistical analysis.

3 | RESULTS

3.1 | Cohort characteristics

The study included 90 men with prostate cancer: 45 with g*ATM* mutations and 45 with g*BRCA2* mutations. Specific mutations in g*ATM* and g*BRCA2* genes are documented in Figure 1. Baseline characteristics, including age, PSA, Gleason Grade Group, were similar in the g*ATM* and g*BRCA2* cohorts (Table 1). A similar number of patients had a family history of cancer, meeting Prostate Cancer NCCN Guidelines[20] for germline testing. Distribution of pathology patterns (e.g., cribriform, neuroendocrine), definitive treatment, and anatomical sites of metastases were also similar between the two cohorts. The median follow-up time since diagnosis was 11.8 years in the g*ATM* cohort and 8.0 years in the g*BRCA2* cohort. Metastases developed in 23/28 g*ATM* and 20/28 g*BRCA2* patients after a median follow-up of 15.7 and 15.0 years, respectively, for the subgroup of men diagnosed with localized prostate cancer. Of the 12 men in the g*ATM* cohort and 14 men in the g*BRCA2* cohort for whom tumor sequencing results were available, none were reported to have somatic alterations in other HR genes.

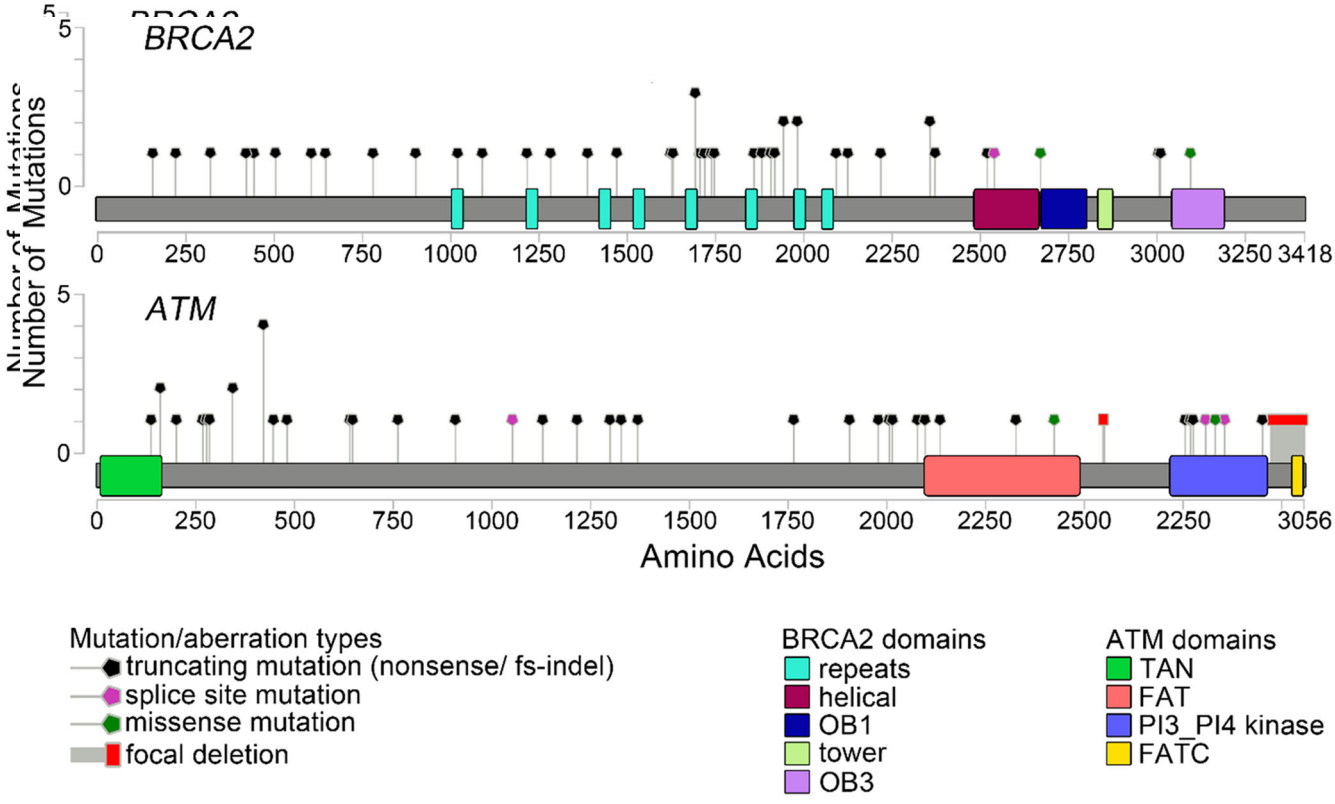


FIGURE 1 Distribution of *ATM* and *BRCA2* mutations [Color figure can be viewed at wileyonlinelibrary.com]

3.2 | PSA_{50} response rates

Responses to systemic therapies in the mCRPC setting, as measured by PSA_{50}, are summarized in Table 2. Comparing patients with g*ATM* versus g*BRCA2* mutations, there was no evident difference in PSA_{50} response to abiraterone: 9/16 (56%) versus 11/19 (58%); to enzalutamide: 9/16 (56%) versus 8/12 (67%); or to docetaxel: 9/13 (69%) versus 9/16 (60%). Only 1 of 3 patients with g*ATM* versus 5 of 7 patients with g*BRCA2* responded to platinum, numbers are too small to draw conclusions. In contrast, there appeared to be a difference in responses to PARPi—0/7 (0%) patients with g*ATM* mutations responded versus 12/14 (86%) patients with g*BRCA2* mutations ($p < .001$).

TABLE 1 Patient characteristics

Characteristics	g*ATM*	g*BRCA2*	*p*
Number of patients	45	45	
Stage M1 at diagnosis (%)	17 (38)	17 (38)	
Age (median [IQR])	58 [54, 66]	62 [55, 67]	.2
PSA (median [IQR])	24 [9, 76]	11 [6, 46]	.13
Grade (%)			
2	6 (17)	4 (11)	
3	7 (20)	5 (14)	
4	5 (14)	8 (22)	
5	17 (49)	20 (54)	
Family history of cancer meeting Prostate Cancer NCCN Guidelines for germline testing[20] (%)	25 (60)	29 (71)	.4
Known other primary cancers (%)	5 (11)	4 (9)	>.9
Pathology (%)			
acinar	24 (80)	22 (76)	
ductal	3 (10)	3 (10)	
intraductal	0 (0)	1 (3)	
cribriform	1 (3)	1 (3)	
neuroendocrine	2 (7)	2 (7)	
Prostatectomy (%)	20 (44)	22 (50)	.7
Radiotherapy (%)	22 (51)	24 (56)	.8
Bone metastasis at the time of diagnosis (%)	14 (31)	15 (33)	>.9
Nodal metastasis at the time of diagnosis (%)	13 (29)	11 (24)	.8
Visceral metastasis at the time of diagnosis (%)	1 (2)	3 (7)	.6

3.3 | Time on treatment

Median time on mCRPC treatment for the g*ATM* and g*BRCA2* cohorts is shown in Table 3. Overall, for abiraterone, enzalutamide, and docetaxel, there was no evidence of different duration from the start to the end of treatment between the cohorts. In the mCRPC setting, median (95% confidence interval [CI]) time on AR-targeted therapies in g*ATM* compared to g*BRCA2* cohort was 9.7 (6.5–23) versus 6.4 (5.4–15.5) months for abiraterone ($p = .5$); 6.5 (4.6-not reached) vs 9 (4.9-not reached) months for enzalutamide ($p > .9$); and 5.1 (3.7-not reached) versus 4 (3–6) months for docetaxel-based chemotherapy ($p = .06$). Median time on platinum-based chemotherapy in the mCRPC setting was 3 (1-not reached) months in the g*ATM* cohort compared to 6 (4-not reached) months in the g*BRCA2* cohort ($p = .11$). We observed a difference in treatment duration on PARPi: 3 (2-not reached) months in the g*ATM* cohort compared to 12 (6.9-not reached) months in the g*BRCA2* cohort ($p = .004$). Time on treatment for each therapy is shown in Figures 5SA–SE.

3.4 | Overall survival

During the study follow-up period, 15/45 (33.3%) g*ATM* and 18/45 (40%) g*BRCA2* patients died. Median (95% CI) OS from diagnosis to death was 10.9 years (9.5-not reached) versus 9.9 years (7.1-not reached, $p = .07$) for the g*ATM* and g*BRCA2* cohorts, respectively (Figure 2). There was no evidence of OS difference between g*ATM* and g*BRCA2* cohorts when analyzing subgroups of patients initially diagnosed with localized (not reached vs 9.9 years, respectively, $p = .07$) or metastatic disease (8.7 vs. 3.6 years, respectively, $p = .4$; Figure S3).

TABLE 2 PSA_{50} response

Therapy	Prior	*gATM*	*gBRCA2*	*p*
Abiraterone	Overall	9/16 (56%)	11/19 (58%)	>.9
	Pre-enza	9/14 (64%)	10/17 (59%)	
	Post-enza	0/2 (0%)	1/2 (50%)	
Enzalutamide	Overall	9/16 (56%)	8/12 (67%)	.7
	Pre-abi	7/10 (70%)	5/7 (71%)	
	Post-abi	2/6 (33%)	3/5 (60%)	
Docetaxel	Overall	9/13 (69%)	9/16 (56%)	.7
	Pre-abi/enza	7/9 (78%)	4/7 (57%)	
	Post-abi/enza	2/4 (50%)	5/9 (56%)	
PARPi	Overall	0/7 (0%)	12/14 (86%)	<.001
	Pre-plat	0/3 (0%)	10/11 (91%)	
	Post-plat	0/4 (0%)	2/3 (67%)	

TABLE 3 Time on treatment

Therapy	Setting	*gATM* Number of pts	*gATM* Median time on therapy (95% CI)	*gBRCA2* Number of pts	*gBRCA2* Median time on therapy (95% CI)	*P*
Abiraterone	Overall	19	9.71 (6.5–23)	24	6.44 (5–15.5)	.6
	HSPC	2	3 (3-N/A)	5	6 (5-N/A)	>.9
	CRPC	17	9.71 (6.5–23)	19	6.44 (5.38–15.5)	.5
Enzalutamide	CRPC	16	6.5 (4.62-N/A)	12	9 (4.92-N/A)	>.9
PARPi	CRPC	7	3 (2-N/A)	15	12 (6.9-N/A)	.004
Platinum	CRPC	3	3 (1-N/A)	7	6 (4-N/A)	.11
Docetaxel	Overall	18	4.13 (4–7)	21	4 (3–6)	.12
	HSPC	5	4 (N/A-N/A)	4	4.5 (3-N/A)	.4
	CRPC	13	5.12 (3.7-N/A)	17	4 (3–6)	.06
			Median time to next therapy (CI 95%)		Median time to next therapy (CI 95%)	
	CRPC	13	10.47 (6.47-N/A)	15	7 (4.16–12.82)	.15

Abbreviations: CRPC, castration resistant prostate cancer; HSPC, hormone sensitive prostate cancer; Pts, patients.

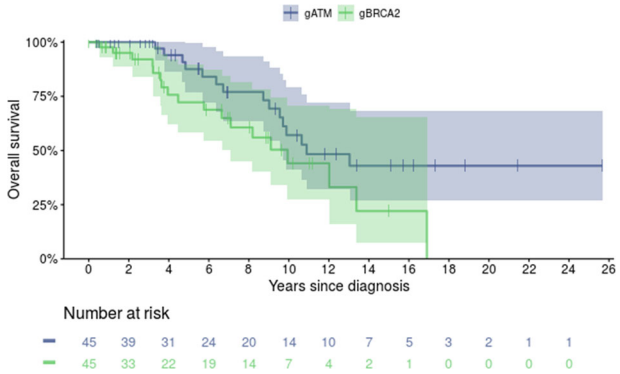


FIGURE 2 Overall survival [Color figure can be viewed at wileyonlinelibrary.com]

Among the 28 patients in each cohort diagnosed with localized prostate cancer, median (95% CI) MFS was 5.7 years (5.1–11.1) versus 5.0 years (4.1–7.0, $p = .13$) for the g*ATM* and g*BRCA2* cohorts, respectively (Figure S4).

4 | DISCUSSION

Prostate tumors with alterations in DDR genes, particularly those in the HR repair pathway, represent a group of interest particularly in light of recent FDA approvals of the PARP inhibitors rucaparib and olaparib. While broadly grouped with g*BRCA1/2* carriers, patients with prostate cancer in the setting of g*ATM* mutations have not been characterized as an independent cohort. This study focuses on patients with prostate cancer and g*ATM* mutations and describes responses to conventional and emerging systemic therapies with the aim of improving our understanding of therapeutic approaches for these patients.

Among men diagnosed with prostate cancer, those carrying g*BRCA2* mutations are recognized to have a more aggressive phenotype (Table S3).[6] Another retrospective study, albeit with limited numbers of g*ATM* carriers, found that g*BRCA1/2* and g*ATM* are associated with earlier age of death and shorter cancer-specific survival.[9] Dedicated attention is warranted for g*ATM* mutation carriers to further define specific prostate cancer risks and response to treatment.

Our data support the concept that while *ATM*-deficient prostate cancer may share features with *BRCA2*-deficient tumors, such as enrichment in the metastatic setting and response to nontargeted agents, they have distinct clinical characteristics. For example, we observed an attenuated response to PARPi in the g*ATM* cohort compared to the g*BRCA2* cohort, consistent with a retrospective study by Marshall et al.,[10] in which 0/8 patients with germline or somatic *ATM* mutations responded to PARPi. This difference in sensitivity to PARPi may partially be explained by different roles for *ATM* and *BRCA2* in the HR repair pathway. ATM's primary role is to recognize double-strand break and to activate downstream HR repair proteins, such as Chk2.[21–23] Once activated, Chk2 has an overlapping function with ATM and phosphorylates the core HR repair pathway effectors, for example, BRCA1, BRCA2.[21] Chk2 can be activated by proteins other than ATM, such as DNA-dependent protein kinase, suggesting that HR repair pathway can be activated even in cells with loss of ATM function.[22] These mechanistic differences in *ATM* and *BRCA2* may account for observed differences in sensitivity to HR-targeted therapies between the two cohorts of our study. In addition, Neeb et al.,[7] have recently reported that ATM protein

expression as measured by ATM IHC is not perfectly overlapping with *ATM* mutations identified by NGS and suggest that protein expression may be another factor for treatment selection, potentially more predictive than DNA sequencing.

Abiraterone, enzalutamide, and docetaxel have mechanisms of action largely independent of *BRCA2* and *ATM*. A previous study reported that these therapies are similarly effective in g*BRCA2* mutation carriers compared to noncarriers and g*BRCA2* mutation carriers might benefit from upfront androgen-directed therapy rather than taxanes.[3] We observed comparable PSA_{50} response rates in the two cohorts in our study. Thus, our data suggest that abiraterone, enzalutamide, and docetaxel should be offered to patients with mCRPC who carry g*ATM* mutations.

Recent data suggest that platinum chemotherapy is effective in patients with *BRCA2* mutations.[24–26] In our study, patients with g*ATM* mutations appeared to have a reduced response to platinum chemotherapy compared to the g*BRCA2* cohort, but this comparison was not statistically significant owing to the small numbers. However, our observations are consistent with other studies reporting disappointing responses to platinum chemotherapy among *ATM* mutation carriers with prostate cancer.[15,26] To date, reported numbers of patients with mCRPC and *ATM* alterations treated with platinum chemotherapy remain small and further studies are needed.

Our data highlight the need to explore new targeted therapies in patients with mCRPC and *ATM* alterations. Preclinical data suggest that *ATM*-deficient prostate tumors may be sensitive to *ATR* inhibitors, which, when combined with PARPi, result in apoptosis in PARPi-resistant prostate cancer cell lines.[7,27] Several ongoing clinical trials are evaluating *ATR* inhibitors in prostate cancer (e.g., NCT04267939, NCT03787680).

We did not observe a significant difference in OS between the two cohorts, although this could be attributable to the limited numbers of patients and deaths and to different proportions of men receiving PARPi in the two groups. More men in g*BRCA2* cohort received PARPi, which has a proven OS benefit for these patients.[12,28]

There are a number of important limitations to our study. First, this is a non-randomized retrospective study with a relatively small sample size. Second, the indications for germline testing in prostate cancer have been and remain evolving, so there are likely differences in practice from 2014 to 2019, as well as ascertainment biases. We attempted to minimize confounding effect by matching cases by year of testing; we acknowledge that men undergoing germline testing 2014–2019 will have been largely those with a strong family history of cancer and/or aggressive phenotype, although both g*ATM* and g*BRCA2* cohorts are likely to have been similarly affected. Third, the two cohorts are matched only for the year of testing, stage at diagnosis and treatment center; other patient characteristics were not matched. Fourth, the study does not include a control group of men without g*ATM* and g*BRCA2* mutations, which limits broader implications for treatment response. Fifth, the study does not include radiographic response assessment or confirmed PSA_{50} responses, limiting treatment response assessments. Clinical practices at different institutions may vary. For example, imaging was performed at clinician discretion without predefined standard intervals, which may have affected the time on treatment and MFS assessments. Finally, somatic alterations in other genes, mutation zygosity and protein expression were not fully addressed, but interference from clonal hematopoiesis of indeterminant potential would be less of an issue.[29] Nevertheless, given the greater prevalence of g*ATM* mutations[30,31] in general population, compared to g*BRCA2* mutations,[32,33] we believe that specific examination of g*ATM* remains important to this patient population.

5 | CONCLUSIONS

Our data provide evidence that standard therapies may be similarly effective in g*ATM*- and g*BRCA2*-associated prostate cancer, whereas PARPi appear less effective in g*ATM*-associated prostate cancer. We did not find that abiraterone, enzalutamide, and docetaxel were less effective in patients with prostate cancer with g*ATM* mutations and thus these agents should remain standard of care options for patients. This important subgroup of patients should continue to be studied and incorporated into clinical trials—especially those incorporating novel agents and combination strategies, for example, ATR inhibitors.

ACKNOWLEDGEMENTS

We thank Agnes Gawne for data collection assistance. We gratefully acknowledge funding support from the Institute for Prostate Cancer Research, Prostate Cancer Foundation, Washington State Medical Oncology Society, Advancing Cancer Treatment, Patrick Walsh Prostate Cancer Research Fund, and NCI award numbers CA097186 (Pacific Northwest Prostate Cancer SPORE), P30 CA015704, P30 CA006973-52, R01 CA238384, R50 CA221836, and T32CA009515; PCF YI VALor award, CDMRP Awards W81XWH-17-2-0043, W81XWH-15-1-0430, PC170503, PC171001, DOD EIRA award W81XWH-17-1-0380 and the DOD Clinical Consortium award W81XWH-16-PCRP-CCRSA.

CONFLICT OF INTERESTS

Catherine H. Marshall: Consulting from Dendreon, Bayer, McGraw-Hill Publishing Company. Travel from Dava Oncology.

Rebeca Lozano: speaker fees from Roche, Janssen, Sanofi and Bayer. Travel support from Roche, Janssen, Sanofi and Astellas Pharma.

Petros Grivas: received grants from Bavarian Nordic, Bristol Myers Squibb, Clovis Oncology, Debiopharm, EMD Serono, GlaxoSmithKline, Immunomedics, Kure It Cancer Research, Merck & Co., Mirati Therapeutics, Pfizer, QED Therapeutics. Dr. Grivas has received consulting fees from AstraZeneca, Astellas Pharma, Bayer, Bristol Myers Squibb, Clovis Oncology, Dyania Health, Driver, EMD Serono, Exelixis, Foundation Medicine, Genentech/Roche, Genzyme, GlaxoSmithKline, Guardant Health, Heron Therapeutics, Immunomedics/Gilead, Infinity Pharmaceuticals, Janssen, Merck &

Co., Mirati Therapeutics, Pfizer, QED Therapeutics, Regeneron Pharmaceuticals, Seattle Genetics, 4D Pharma PLC.Celestia S. Higano: Institutional research funding: Aptevo, Aragon, Astellas, AstraZeneca, Clovis, Dendreon, eFFECTOR Therapeutics, Emergent, Ferring, Genentech, Hoffman-La roche, Medivation, Pfizer; Consulting, scientific advisory boards: Astellas, Bayer, Blue Earth Diagnositics, Clovis, Dendreon, Ferring, Hinova, Janssen, Merck, Orion, Pfizer, Tolmar, Carrick Therapeutics, Novartis, Genentech; Other: spouse holds stock and former officer of CTI Biopharma.

Bruce Montgomery: Institutional research funding: Astellas, AstraZeneca, Beigene, Clovis, Janssen.

Peter S. Nelson: Consultant for Bristol Myers Squibb, Astellas, and Janssen Pharmaceuticals and received fees from UpToDate.

David Olmos: grant research support (to the institution) from AstraZeneca, Astellas, Bayer, Jansen. Advisory board and speaker fees from AstraZeneca, Astellas, Bayer, BioOncotech (Uncompensated), Clovis, Daiichi-Sankyo, Jansen, MSD, Pfizer. Travel support from AstraZeneca, Astellas, Bayer, F. Hoffman La Roche, Genetech, Ipsen, Jansen.

Michael T. Schweizer: Paid consultant for Janssen and Resverlogix. Research funding from Bristol Myers Squibb, Merck, Immunomedics, Janssen, AstraZeneca, Pfizer, Madison Vaccines, Tmunity and Hoffman-La Roche.

Todd A. Yezefski: consultant for Dendreon.

Evan Y. Yu: Consulting—Advanced Accelerator Applications, Bayer, Clovis, Janssen, Merck. Research to institution—Bayer, Blue Earth, Dendreon, Merck, Taiho.

Oliver Sartor: Grant support to institution for AAA Pharma, AstraZeneca, Bayer, Endocyte, Progenics, Novartis, and Janssen, consulting fees from Astellas, Blue Earth Diagnostics, EMD Serono, Pfizer, Constellation, Dendreon, Bristol-Myers Squibb, Invitae, Merck, Innocrin, and Sotio, Consulting fees from AAA Pharma, AstraZeneca, Bayer, Endocyte, Progenics, Novartis, Janssen, Astellas, Blue Earth Diagnostics, EMD Serono, Pfizer, Constellation, Noria Therapeutics, Clovis, Myriad, Noxopharm, Point Biopharm, Tenebio, Theragnostics, Telix, Clarity Pharmaceuticals, and Fusion.

Elena Castro: honoraria and consulting CLOVIS, AstraZeneca, Astellas, Jansen, MSD, Roche, Pfizer; research funding AstraZeneca, Bayer, Janssen, travel accommodations AstraZeneca, Bayer, Janssen.

Emmanuel S. Antonarakis: has served as a paid consultant/advisor for Invitae, Janssen, Pfizer, Sanofi, Dendreon, Merck, Bristol-Myers Squibb, AstraZeneca, Clovis, Bayer, Constellation, Eli Lilly and Amgen; and has received research funding to his institution from Janssen, Johnson & Johnson, Sanofi, Dendreon, Genentech, Novartis, Bayer, Merck, Bristol-Myers Squibb, AstraZeneca, ESSA and Constellation.

Heather H. Cheng; Research funding to institution from Clovis, Janssen, Sanofi, Medivation/Astellas, Color Foundation; Consultancy to AstraZeneca; Royalties from up to date. The other authors declare that there are no conflict of interests.

ETHICS STATEMENT

This study was approved by IRB board at each participating site.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

ORCID

Alexandra O. Sokolova http://orcid.org/0000-0003-0821-6503
Roman Gulati http://orcid.org/0000-0002-7592-6567
Elisa M. Ledet http://orcid.org/0000-0003-1230-3255
Michael T. Schweizer http://orcid.org/0000-0002-5510-0661
Channing J. Paller http://orcid.org/0000-0003-3658-1858
Oliver Sartor http://orcid.org/0000-0002-8777-7343
Emmanuel S. Antonarakis http://orcid.org/0000-0003-0031-9655
Heather H. Cheng http://orcid.org/0000-0002-1365-0702

REFERENCES

1. Pritchard CC, Mateo J, Walsh MF, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. *N Engl J Med*. 2016;375:443-453.
2. Nicolosi P, Ledet E, Yang S, et al. Prevalence of germline variants in prostate cancer and implications for current genetic testing guidelines. *JAMA Oncol*. 2019;5:523-528.
3. Castro E, Romero-Laorden N, Del Pozo A, et al. PROREPAIR-B: a prospective cohort study of the impact of germline DNA repair mutations on the outcomes of patients with metastatic castration-resistant prostate cancer. *J Clin Oncol*. 2019;37:490-503.
4. Cheng HH, Sokolova AO, Schaeffer EM, Small EJ, Higano CS. Germline and somatic mutations in prostate cancer for the clinician. *J Natl Compr Canc Netw*. 2019;17:515-521.
5. Page EC, Bancroft EK, Brook MN, et al. Interim results from the IMPACT Study: evidence for prostate-specific antigen screening in BRCA2 mutation carriers. *Eur Urol*. 2019;76:831-842.
6. Castro E, Goh C, Olmos D, et al. Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. *J Clin Oncol*. 2013;31:1748-1757.
7. Neeb A, Herranz N, Arce-Gallego S, et al. Advanced prostate cancer with ATM loss: PARP and ATR inhibitors. *Eur Urol*. 2020;0:200-211.
8. Carter HB, Helfand B, Mamawala M, et al. Germline mutations in ATM and BRCA1/2 are associated with grade reclassification in men on active surveillance for prostate cancer. *Eur Urol*. 2018;75:743-749. https://doi.org/10.1016/j.eururo.2018.09.021
9. Na R, Zheng SL, Han M, et al. Germline mutations in ATM and BRCA1/2 distinguish risk for lethal and indolent prostate cancer and are associated with early age at death. *Eur Urol*. 2017;71:740-747.
10. Marshall CH, Sokolova AO, McNatty AL, et al. Differential response to olaparib treatment among men with metastatic castration-resistant prostate cancer harboring BRCA1 or BRCA2 Versus ATM mutations. *Eur Urol*. 2019;76:452-458.
11. Abida W, Patnaik A, Campbell D, et al. Rucaparib in men with metastatic castration-resistant prostate cancer harboring a BRCA1 or BRCA2 Gene Alteration. *J Clin Oncol*. 2020;20:01035-03772. https://doi.org/10.1200/JCO.20.01035
12. De Bono J, Mateo J, Fizazi K, et al. Olaparib for metastatic castration-resistant prostate cancer. *N Engl J Med*. 2020;382:2091-2102.
13. Sokolova AO, Yu EY, Cheng HH. Honing in on PARPi response in prostate cancer: from HR pathway to gene-by-gene granularity. *Clin Cancer Res*. 2020;26:2439-2440.
14. Athie A, Arce-Gallego S, Gonzalez M, et al. Targeting DNA repair defects for precision medicine in prostate cancer. *Curr Oncol Rep*. 2019;21:42.
15. Mota JM, Barnett E, Nauseef JT, et al. Platinum-based chemotherapy in metastatic prostate cancer with DNA repair gene alterations. *JCO Precis Oncol*. 2020;4:355-366. https://doi.org/10.1200/PO.19.00346

16. Abida W, Campbell D, Patnaik A, et al. Non-BRCA DNA damage repair gene alterations and response to the PARP inhibitor rucaparib in metastatic castration-resistant prostate cancer: analysis from the phase II TRITON2 Study. *Clin Cancer Res*. 2020;26:2487-2496.
17. Carlson AS, Acevedo RI, Lim DM, et al. Impact of mutations in homologous recombination repair genes on treatment outcomes for metastatic castration resistant prostate cancer. *PLoS One*. 2020;15:0239686.
18. Karbassi I, Maston GA, Love A, et al. A standardized DNA variant scoring system for pathogenicity assessments in mendelian disorders. *Hum Mutat*. 2016;37:127-134.
19. Scher HI, Morris MJ, Stadler WM, et al. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the prostate cancer clinical trials working group 3. *J Clin Oncol*. 2016;34:1402-1418.
20. National Comprehensive Cancer Network. Prostate Cancer (Version 2.2020). https://www.nccn.org/professionals/physician_gls/pdf/prostate_blocks.pdf. Accessed November 10, 2020.
21. Zannini L, Delia D, Buscemi G. CHK2 kinase in the DNA damage response and beyond. *J Mol Cell Biol*. 2014;6:442-457.
22. Li J, Stern DF. Regulation of CHK2 by DNA-dependent protein kinase. *J Biol Chem*. 2005;280:12041-12050.
23. Lavin MF, Delia D, Chessa L. ATM and the DNA damage response. Workshop on ataxia-telangiectasia and related syndromes. *EMBO Rep*. 2006;7:154-160.
24. Pomerantz MM, Spisák S, Jia L, et al. The association between germline BRCA2 variants and sensitivity to platinum-based chemotherapy among men with metastatic prostate cancer. *Cancer*. 2017;123:3532-3539.
25. Cheng HH, Pritchard CC, Boyd T, Nelson PS, Montgomery B. Biallelic inactivation of BRCA2 in platinum sensitive, metastatic castration resistant prostate cancer. *Eur Urol*. 2016;69:992-995.
26. Schmid S, Omlin A, Higano C, et al. Activity of platinum-based chemotherapy in patients with advanced prostate cancer with and without DNA repair gene aberrations. *JAMA Netw. Open*. 2020;3:e2021692.
27. Rafiei S, Fitzpatrick K, Liu D, et al. ATM loss confers greater sensitivity to ATR inhibition than PARP inhibition in prostate cancer. *Cancer Res*. 2020;80:2094-2100.
28. Hussain M, Mateo J, Fizazi K, et al. Survival with olaparib in metastatic castration-resistant. *N Engl J Med*. 2020;383:2345-2357.
29. Sokolova AO, Shirts BH, Konnick EQ, et al. Complexities of next-generation sequencing in solid tumors: case studies. *J Natl Compr Canc Netw*. 2020;18:1150-1155.
30. Broeks A, Urbanus JH, Floore AN, et al. ATM-heterozygous germline mutations contribute to breast cancer–susceptibility. *Am J Hum Genet*. 2000;66:494-500.
31. Hall MJ, Bernhisel R, Hughes E, et al. Germline pathogenic variants in the ataxia telangiectasia mutated (ATM) gene are associated with high and moderate risks for multiple. *Cancers. Cancer Prev Res (Phila. Pa)*. 2021;14:433-440.
32. Maxwell KN, Domchek SM, Nathanson KL, Robson ME. Population frequency of germline BRCA1/2 mutations. *J Clin Oncol*. 2016;34:4183-4185.
33. Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. Br. J. Cancer 83, 1301–1308 (2000).

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Sokolova AO, Marshall CH, Lozano R, et al. Efficacy of systemic therapies in men with metastatic castration resistant prostate cancer harboring germline *ATM* versus *BRCA2* mutations. *The Prostate*. 2021;81:1382-1389. https://doi.org/10.1002/pros.24236

PRECISION MEDICINE

original reports abstract

Differential Activity of PARP Inhibitors in *BRCA1*- Versus *BRCA2*-Altered Metastatic Castration-Resistant Prostate Cancer

Fadi Taza, MD[1,2]; Albert E. Holler, BA[1]; Wei Fu, PhD[1]; Hao Wang, PhD[1]; Nabil Adra, MD[3]; Costantine Albany, MD[3]; Ryan Ashkar, MD[3]; Heather H. Cheng, MD[4]; Alexandra O. Sokolova, MD[4]; Neeraj Agarwal, MD[5]; Adam Kessel, MD[5]; Alan Bryce, MD[6]; Nellie Nafissi, MD[6]; Pedro Barata, MD[7]; A. Oliver Sartor, MD[7]; Diogo Bastos, MD[8]; Oren Smaletz, MD[9]; Jacob E. Berchuck, MD[10]; Mary-Ellen Taplin, MD[10]; Rahul Aggarwal, MD[11]; Cora N. Sternberg, MD[12]; Panagiotis J. Vlachostergios, MD[12]; Ajjai S. Alva, MD[13]; Christopher Su, MD[13]; Catherine H. Marshall, MD[1]; and Emmanuel S. Antonarakis, MD[1]

PURPOSE Two poly (ADP-ribose) polymerase (PARP) inhibitors (olaparib and rucaparib) are US Food and Drug Administration–approved for patients with metastatic castration-resistant prostate cancer (mCRPC) harboring *BRCA1/2* mutations, but the relative efficacy of PARP inhibition in *BRCA1*- versus *BRCA2*-altered mCRPC is understudied.

METHODS We conducted a multicenter retrospective analysis involving 12 sites. We collected genomic and clinical data from 123 patients with *BRCA1/2*-altered mCRPC who were treated with PARP inhibitors. The primary efficacy end point was the prostate-specific antigen (PSA) response (≥ 50% PSA decline) rate. Secondary end points were PSA progression-free survival (PSA-PFS), clinical or radiographic PFS, and overall survival. We compared clinical outcomes, and other genomic characteristics, among *BRCA1*- versus *BRCA2*-altered mCRPC.

RESULTS A total of 123 patients (13 *BRCA1* and 110 *BRCA2*) were included. PARP inhibitors used were olaparib (n = 116), rucaparib (n = 3), talazoparib (n = 2), and veliparib (n = 2). At diagnosis, 72% of patients had Gleason 8-10 disease. *BRCA1* patients were more likely to have metastatic disease at presentation (69% *v* 37%; *P* = .04). Age, baseline PSA, metastatic distribution, and types of previous systemic therapies were similar between groups. There were equal proportions of germline mutations (51% *v* 46%; *P* = .78) in both groups. *BRCA1* patients had more monoallelic (56% *v* 41%; *P* = .49) and concurrent *TP53* (55% *v* 36%; *P* = .32) mutations. PSA_{50} responses in *BRCA1*- versus *BRCA2*-altered patients were 23% versus 63%, respectively (*P* = .01). *BRCA2* patients achieved longer PSA-PFS (HR, 1.94; 95% CI, 0.92 to 4.09; *P* = .08), PFS (HR, 2.08; 95% CI, 0.99 to 4.40; *P* = .05), and overall survival (HR, 3.01; 95% CI, 1.32 to 6.83; *P* = .008). Biallelic (compared with monoallelic) mutations, truncating (compared with missense) mutations, and absence of a concurrent *TP53* mutation were associated with PARP inhibitor sensitivity.

CONCLUSION PARP inhibitor efficacy is diminished in *BRCA1*- versus *BRCA2*-altered mCRPC. This is not due to an imbalance in germline mutations but might be related to more monoallelic mutations and/or concurrent *TP53* alterations in the *BRCA1* group.

JCO Precis Oncol 5:1200-1220. © 2021 by American Society of Clinical Oncology

INTRODUCTION

Metastatic castration-resistant prostate cancer (mCRPC) remains a lethal disease with a poor prognosis.[1] Germline or somatic mutations in DNA damage repair genes have been described in approximately 20%-25% of these patients, which include *BRCA1* and *BRCA2*.[2,3] Although patients with these mutations generally have more aggressive disease and higher mortality than those with proficient homologous recombination repair (HRR),[4,5] they also present as a novel therapeutic opportunity. Poly (ADP-ribose) polymerase (PARP) inhibitors efficiently kill tumor cells by synthetic lethality in cancers with damaged *BRCA1* or *BRCA2* genes, with PARP-mediated repair pathway inhibition resulting in DNA disruption and, therefore, genomic instability causing cancer cell death.[6,7]

In May 2020, the US Food and Drug Administration approved two PARP inhibitors (olaparib and rucaparib) for men with mCRPC harboring a germline or somatic mutation in a gene associated with HRR.[8] The approval of olaparib was based on the PROfound study in which men with previously treated mCRPC and HRR deficiency (mutation in one of the 14 HRR genes) who received olaparib had improved progression-free survival and overall survival relative to next-generation hormone therapy (enzalutamide and abiraterone).[9,10] The approval of rucaparib was based on the TRITON2 trial, which reported prostate-specific antigen (PSA) and objective response rates of 63 and 44 percent in men with previously treated mCRPC and somatic or germline *BRCA1* and *BRCA2* mutations, respectively.[11] One of the most interesting post hoc findings from

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on June 11, 2021 and published at ascopubs.org/journal/po on July 22, 2021: DOI https://doi.org/10.1200/PO.21.00070

CONTEXT

Key Objective

We conducted a multicenter retrospective study to determine whether the efficacy of poly (ADP-ribose) polymerase (PARP) inhibitors differs between cancers with *BRCA1* and *BRCA2* mutations and to examine differences in other genomic alterations that coexist with *BRCA1/2* mutations.

Knowledge Generated

We show that PARP inhibitor efficacy is diminished in *BRCA1*- versus *BRCA2*-altered metastatic castration-resistant prostate cancer. This is not due to an imbalance in germline mutations but might be related to more monoallelic mutations and/or concurrent *TP53* alterations in the *BRCA1* group.

Relevance

Additional therapeutic approaches are needed for patients with *BRCA1*-altered prostate cancer. These findings may have broad implications for other *BRCA1/2*-associated malignancies (breast, ovarian, and pancreatic cancers) where PARP inhibitors are used.

TRITON2 study was the possible disparity in the effectiveness of rucaparib in men with *BRCA1* relative to *BRCA2* mutations. More precisely, the therapeutic activity of rucaparib appeared to be generally higher in *BRCA2*-altered compared with *BRCA1*-altered mCRPC tumors, although formal statistical analyses comparing outcomes by gene mutation were not conducted. Similar trends were observed in the PROfound study, which also suggested dampened activity of olaparib in the *BRCA1* population.[10]

The activity of rucaparib was also previously explored in patients with mCRPC harboring non-*BRCA1/2* HRR gene mutations and was not sufficient to merit regulatory approval for that molecular subset of patients[12]; similar observations have been made with olaparib in the gene-by-gene post hoc analyses from the PROfound study.[9,10] However, differences in PARP inhibitor sensitivity between patients with *BRCA1*- and *BRCA2*-mutated mCRPC have not been formally examined to date. We hypothesized that patients with *BRCA1* mutations would not exhibit the same responses to PARP inhibition as patients with *BRCA2* mutations. Here, we describe the differential sensitivity to treatment with PARP inhibitors among men with *BRCA1* versus *BRCA2* mutations.

METHODS

Study Population and Design

This was a multicenter retrospective analysis of 123 consecutive patients from 12 academic sites with mCRPC who received single-agent PARP inhibitor treatment between December 2014 and July 2020. All PARP inhibitors were permitted in this analysis. Only patients harboring deleterious (somatic or germline) mutations in *BRCA1* or *BRCA2* were included in the study; other HRR genes were excluded. All centers participating in the study obtained local institutional review board approval before data abstraction.

Deleterious mutations in *BRCA1/2* were defined as any alterations resulting in protein truncation (frameshift or nonsense mutations, canonical splice-site mutations, and truncating rearrangements) or homozygous genomic deletions. Selected missense mutations in *BRCA1/2* were also classified as deleterious, but only if they were designated as pathogenic or likely pathogenic in the ClinVar and/or COSMIC databases. All other alterations were considered variants of unknown significance and were excluded. Mutation origin (germline or somatic) and zygosity status (monoallelic or biallelic) were also recorded.

Study Outcomes

Demographic, clinical, and genomic characteristics were collected for all patients. This included age, Gleason score, PSA level, stage at diagnosis, metastatic distribution, and the type and number of previous systemic therapies received. We also captured information on concurrent genomic alterations in key prostate cancer genes (namely, *TP53*, *PTEN*, *RB1*, *SPOP*, *AR*, and *TMPRSS2-ERG*).

The primary efficacy end point was the percentage of men achieving a confirmed $\geq$ 50% decline in PSA level from baseline at the initiation of PARP inhibitor treatment (PSA_{50} response). Secondary end points were PSA progression-free survival (PSA-PFS, defined as the time until a $\geq$ 25% increase in PSA from baseline or nadir), progression-free survival (PFS, defined as the time to investigator-assessed clinical or radiographic progression, excluding PSA progression), and overall survival (OS, defined as the time to death from any cause). These definitions are broadly consistent with the Prostate Cancer Working Group 3 guidelines.[13]

Statistical Analysis

The desired sample size was prospectively defined, on the basis of the primary end point. In the published literature, the prevalence of *BRCA2* mutations relative to *BRCA1* mutations in prostate cancer is approximately 9:1.[14,15] We hypothesized that the PSA_{50} response rate to PARP inhibition would be 60% in *BRCA2*-mutated prostate cancers

and 20% in *BRCA1*-mutated prostate cancers. To achieve 80% power to detect this difference using Fisher's exact test with a one-sided alpha of .05, we would need to collect at least a total of 120 patients (108 with a *BRCA2* mutation and 12 with a *BRCA1* mutation).

PSA_{50} response rates were compared between *BRCA1*- and *BRCA2*-altered patients using logistics regression. Time-to-event outcomes of PSA-PFS, PFS, and OS were estimated using Kaplan-Meier method, and comparisons between groups were carried out using Cox proportional-hazards model. Multivariable logistic regression and Cox models were used to estimate odds ratio (OR) for PSA response and hazard ratios (HRs) for time-to-event outcomes and corresponding 95% CIs and to test for the association between *BRCA* mutation and patient outcomes, after adjusting for important clinical variables of age, Gleason sum, M stage, baseline PSA, and previous taxane treatment. Separate multivariable models were used to estimate the association between *BRCA1/2* mutations and clinical outcomes adjusting for *TP53* and *PTEN* mutations. The database was locked on August 30, 2020. Patients not meeting one or more of the time-to-event end points at the time of database lock were censored for that end point at the time of the last contact with the health system. R 4.0.1 was used for statistical analyses. All tests were two-sided, and *P* values of $\leq$ .05 were considered statistically significant; adjustments were not made for multiple statistical comparisons.

RESULTS

Cohort Characteristics

One hundred twenty-three consecutive mCRPC patients with deleterious mutations in *BRCA1* (n = 13) or *BRCA2* (n = 110) were included in this analysis. Most mutations were frameshift alterations (58%), followed by homozygous deletions (13%); missense alterations were found in 8.1% of cases. PARP inhibitors used were olaparib (n = 116), rucaparib (n = 3), talazoparib (n = 2), and veliparib (n = 2). Table 1 displays the baseline demographic, clinical, and genomic characteristics of these patients. Men with *BRCA1* mutations did not significantly differ from those with *BRCA2* mutations, except that more patients in the *BRCA1* group had metastatic disease at initial diagnosis (69% *v* 37% *P* = .04). In the overall cohort, 72% of patients had Gleason 8-10 disease, the median age at the time of PARP inhibitor initiation was 67 years (interquartile range 61-71), and the median baseline PSA level was 44.3 ng/mL (interquartile range 8.7-140). Germline (compared with somatic) *BRCA1/2* mutations were equally distributed in the two groups. There were numerically more monoallelic mutations (56% *v* 41%; *P* = .49) and more concurrent *TP53* mutations (55% *v* 36%; *P* = .32) in the *BRCA1* group, but broadly similar numbers of mutations in other key genes (*PTEN*, *RB1*, *SPOP*, *TMPRSS2-ERG*, and *AR*) across groups (Fig 1). Differences in the mechanisms of biallelic inactivation among the *BRCA1*- versus *BRCA2*-altered cancers are summarized in Appendix Table A1 and Figure A1.

Relationship Between *BRCA1/2* and *TP53* Mutations

To further explore the potential relationship between *BRCA1/2* mutations and concurrent *TP53* mutations, we interrogated the cBioPortal for Cancer Genomics database[16] that contains DNA sequencing analysis on 6,875 patients with prostate cancer. Of those, 49 (0.7%) had deleterious *BRCA1* mutations or deletions and 323 (4.7%) had deleterious *BRCA2* alterations. With respect to *TP53*, 39% of *BRCA1*-altered (19 of 49) and 22% of *BRCA2*-altered (71 of 323) prostate cancers also harbored a deleterious *TP53* mutation (*P* for difference, .019). There were no differences with respect to concurrent *PTEN* alterations; 20% of *BRCA1*-altered (10 of 49) and 17% of *BRCA2*-altered (55 of 323) prostate cancers also harbored a *PTEN* alteration (*P* for difference, .548). Conversely, *RB1* mutations or deletions were enriched in *BRCA2*-altered cases; 12% of *BRCA1*-altered (6 of 49) and 30% of *BRCA2*-altered (97 of 323) prostate cancers also harbored an *RB1* alteration (*P* for difference, .001).

We then examined the association between *BRCA1/2* mutations and concurrent *TP53* mutations in the other *BRCA*-associated cancers, again using cBioPortal.[16] Among 9,134 patients with breast cancer, 50% of *BRCA1*-altered (144 of 288) and 41% of *BRCA2*-altered (143 of 350) breast cancers also harbored deleterious *TP53* mutations (*P* for difference, .025). Similarly, among 1,206 patients with pancreatic cancer, 56% of *BRCA1*-altered (14 of 25) and 44% of *BRCA2*-altered (7 of 16) pancreatic cancers also harbored deleterious *TP53* mutations, although this did not reach significance (*P* for difference, .328). Conversely, among 1,668 patients with ovarian cancer, the prevalence of concurrent *TP53* mutations was very high in both *BRCA1*-altered (94%; 77 of 82) and *BRCA2*-altered (94%; 80 of 85) ovarian cancers (*P* for difference, .604).

PSA Response Rate

The best PSA response for each patient (at any time) is depicted in Figure 2A. Overall, 72 of 123 patients (59%) achieved a PSA_{50} response to PARP inhibitor treatment. There were significantly fewer PSA_{50} responses in patients with *BRCA1*-altered versus *BRCA2*-altered mCRPC (23% *v* 63% respectively; OR, 0.18; 95% CI, 0.04 to 0.62; *P* = .01). This difference persisted after adjusting for age, Gleason sum, stage, baseline PSA, and previous taxane treatment (adjusted OR, 0.20; 95% CI, 0.04 to 0.76; *P* = .03) and after adjusting for concurrent *TP53* and *PTEN* mutations (adjusted OR, 0.22; 95% CI, 0.05 to 0.86; *P* = .04; Table 2). Paradoxically, the median time to best PSA response (in those who achieved a response) was shorter in the *BRCA1* than the *BRCA2* group (6 *v* 17 weeks; *P* < .01). A forest plot showing other clinical and molecular factors that influenced PSA_{50} responses is depicted in Figure 3A. PSA_{50}

TABLE 1. Baseline Demographic, Clinical, and Genomic Data Overall and by Mutation Type

Characteristic	Overall Patients, No. (%)	*BRCA1* Patients, No. (%)	*BRCA2* Patients, No. (%)	*P*
Gleason sum at diagnosis	123	13	110	.01
8-10	89 (72.4)	10 (76.9)	79 (71.8)	
6-7	25 (20.3)	0 (0)	25 (22.7)	
Unknown	9 (7.3)	3 (23.1)	6 (5.5)	
Age at start of therapy, years	123	13	110	.07
Median/mean	67/66.1	71/69.9	66.5/65.6	
Min-max	46-91	57-86	46-91	
Q1-Q3	61-71	67-73	60.2-71	
Baseline PSA, ng/mL	123	13	110	.3
Median/mean	44.3/281.3	47.2/172.3	43.8/294.1	
Min-max	0-6,394.9	0-1,459	0-6,394.9	
Q1-Q3	8.7-140.4	4.3-137.7	9.1-179.8	
T stage at diagnosis	85	8	77	1
T1-T2	31 (36.5)	3 (37.5)	28 (36.4)	
T3-T4	54 (63.5)	5 (62.5)	49 (63.6)	
N stage at diagnosis	123	13	110	.7
N0	100 (81.3)	10 (76.9)	90 (81.8)	
N1	23 (18.7)	3 (23.1)	20 (18.2)	
M stage at diagnosis	123	13	110	.03
M0	73 (59.3)	4 (30.8)	69 (62.7)	
M1	50 (40.7)	9 (69.2)	41 (37.3)	
Prior docetaxel or cabazitaxel	123	13	110	.2
No	49 (39.8)	3 (23.1)	46 (41.8)	
Yes	74 (60.2)	10 (76.9)	64 (58.2)	
Prior enzalutamide or abiraterone	123	13	110	1
No	14 (11.4)	1 (7.7)	13 (11.8)	
Yes	109 (88.6)	12 (92.3)	97 (88.2)	
Presence of bone metastases	119	13	106	1
No	16 (13.4)	1 (7.7)	15 (14.2)	
Yes	103 (86.6)	12 (92.3)	91 (85.8)	
Presence of visceral metastases	119	13	106	.3
No	91 (76.5)	12 (92.3)	79 (74.5)	
Yes	28 (23.5)	1 (7.7)	27 (25.5)	
Presence of nodal metastases	119	13	119	1
No	54 (45.4)	6 (46.2)	48 (45.3)	
Yes	65 (54.6)	7 (53.8)	58 (54.7)	
Origin of mutation	123	13	110	.7
Germline	62 (50.4)	6 (46.2)	56 (50.9)	
Somatic	61 (49.6)	7 (53.8)	54 (49.1)	
Allelic status of mutation	89	9	80	.49
Monoallelic	38 (42.7)	5 (55.6)	33 (41.2)	
Biallelic	51 (57.3)	4 (44.4)	47 (58.8)	

(Continued on following page)

TABLE 1. Baseline Demographic, Clinical, and Genomic Data Overall and by Mutation Type (Continued)

Characteristic	Overall Patients, No. (%)	*BRCA1* Patients, No. (%)	*BRCA2* Patients, No. (%)	*P*
Mutation mechanism	123	13	110	.001
Frameshift	71 (57.7)	3 (23.1)	68 (61.8)	
Homozygous deletion	16 (13)	0 (0)	16 (14.5)	
Missense	10 (8.1)	4 (30.8)	6 (5.5)	
Nonsense	12 (9.8)	3 (23.1)	9 (8.2)	
Rearrangement	11 (8.9)	2 (15.4)	9 (8.2)	
Splicing	3 (2.4)	1 (7.7)	2 (1.8)	
Concurrent *TP53* mutation	103	11	92	.32
No	64 (62.1)	5 (45.5)	59 (64.1)	
Yes	39 (37.9)	6 (54.5)	33 (35.9)	
Concurrent *PTEN* mutation	110	11	99	.4
No	87 (79.1)	10 (90.9)	77 (77.8)	
Yes	23 (20.9)	1 (9.1)	22 (22.2)	
Concurrent *RB1* mutation	110	11	99	.2
No	91 (82.7)	11 (100)	80 (80.8)	
Yes	19 (17.3)	0 (0)	19 (19.2)	
Concurrent *SPOP* mutation	110	11	99	1
No	106 (96.4)	11 (100)	95 (96)	
Yes	4 (3.6)	0 (0)	4 (4)	
Concurrent *AR* mutation	109	11	98	.68
No	89 (81.7)	10 (90.9)	79 (80.6)	
Yes	20 (18.3)	1 (9.1)	19 (19.4)	
Concurrent *TMPRSS2-ERG* fusion	110	11	99	1
No	95 (86.4)	10 (90.9)	85 (85.9)	
Yes	15 (13.6)	1 (9.1)	14 (14.1)	

Abbreviations: M, metastasis; N, node; PSA, prostate-specific antigen; T, tumor.

responses were numerically lower in patients with somatic (compared with germline) mutations, monoallelic (compared with biallelic) mutations, missense (compared with truncating) mutations, and concurrent *TP53* mutations.

Time-to-Event Outcomes

The median PSA-PFS with PARP inhibitor treatment was 40.7 weeks (95% CI, 29.3 to 53.0) in the entire cohort. PSA-PFS was shorter in *BRCA1*-mutated compared with

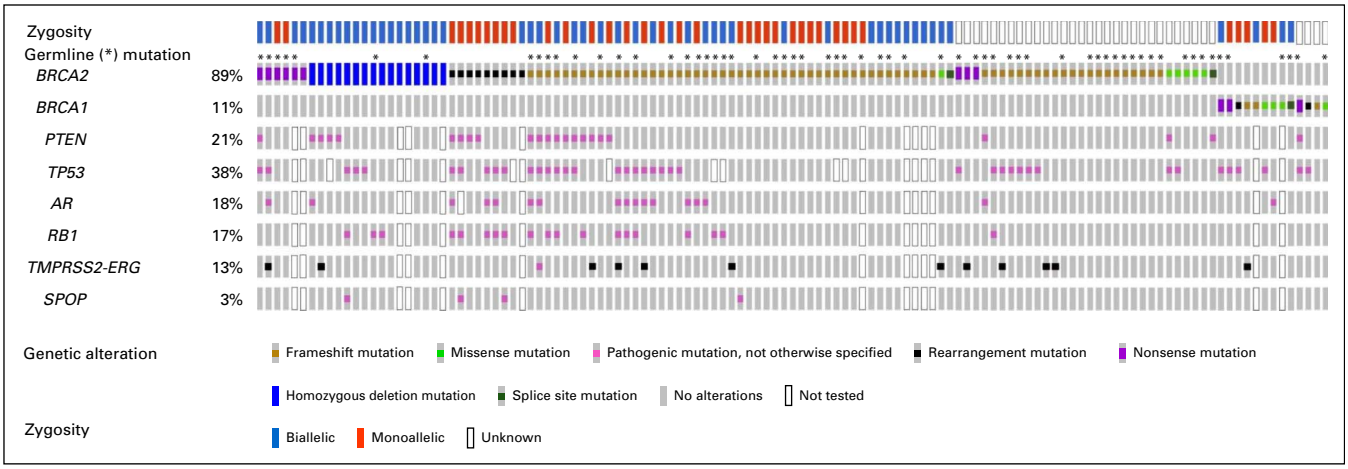


FIG 1. Summary of key genetic alterations identified among patients in the overall cohort (N = 123).

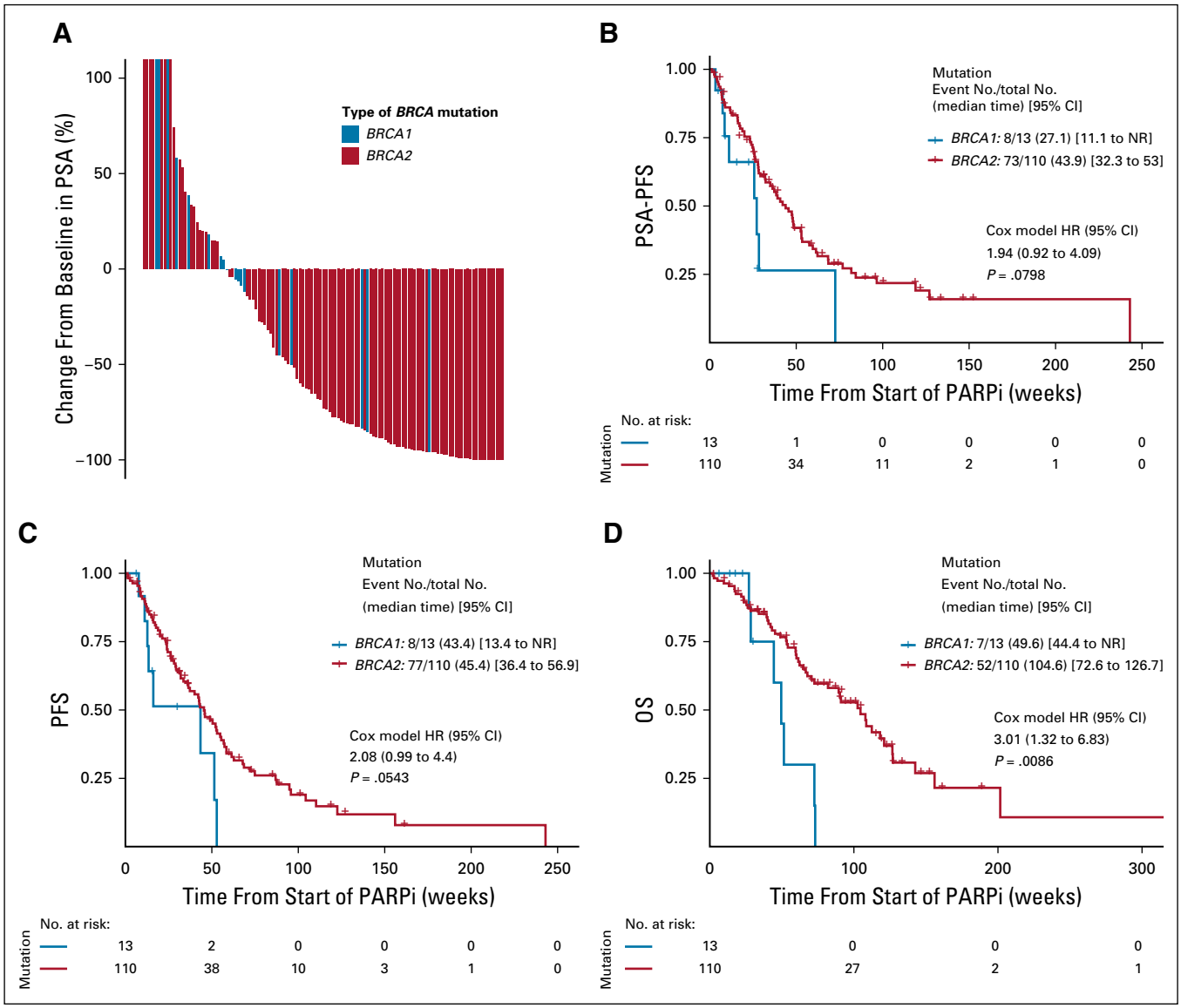


FIG 2. Efficacy outcomes, according to type of *BRCA* mutation. (A) Waterfall plot of best PSA response, comparing *BRCA1*- and *BRCA2*-altered patients. (B) Kaplan-Meier analysis of PSA-PFS, (C) PFS, and (D) OS, comparing *BRCA1*- and *BRCA2*-altered patients. HR, hazard ratio; NR, not reached; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitor; PFS, progression-free survival; PSA, prostate-specific antigen.

BRCA2-mutated patients (median 27.1 *v* 43.9 weeks; HR, 1.94; 95% CI, 0.92 to 4.09; $P = .08$; Fig 2B). This difference weakened after adjusting for age, Gleason sum, stage, baseline PSA, and previous taxane treatment (adjusted HR, 1.63; 95% CI, 0.73 to 3.63; $P = .23$) and after adjusting for concurrent *TP53* and *PTEN* mutations (adjusted HR, 1.40; 95% CI, 0.59 to 3.31; $P = .44$; Table 2). PSA-PFS was numerically shorter in patients with monoallelic (compared with biallelic) mutations, missense (compared with truncating) mutations, and concurrent *TP53* mutations (Fig 3B).

The median PFS was 43.4 weeks (95% CI, 36.0 to 53.0) in the overall cohort. Again, PFS was shorter in *BRCA1*- compared with *BRCA2*-mutated patients (median 43.4 *v* 45.4 weeks; HR, 2.08; 95% CI, 0.99 to 4.40; $P = .05$; Fig 2C). This difference persisted after adjusting for age, Gleason sum, stage, baseline PSA, and previous taxane treatment (adjusted HR, 2.20; 95% CI, 0.96 to 5.04; $P = .06$) and after adjusting for concurrent *TP53* and *PTEN* mutations (adjusted HR, 2.20; 95% CI, 0.97 to 4.96; $P = .06$; Table 2). PFS was numerically shorter in patients with monoallelic mutations, missense mutations, and concurrent *TP53* alterations (Fig 3C).

We also explored PSA-PFS and PFS in the responding patients only, examining *BRCA1* and *BRCA2* patients separately. Overall, 72 of 123 patients achieved a PSA_{50} response: three patients with *BRCA1* and 69 patients with *BRCA2* mutations. Differences in baseline characteristics between the responding and nonresponding patients are

TABLE 2. Multivariable Analyses for PSA_{50} Response, PSA-PFS, PFS, and OS

			Multivariable Analysis of PSA_{50} Response				Multivariable Analysis of PSA-PFS				Multivariable Analysis of PFS				Multivariable Analysis of OS			
Name	**Levels**	**Reference**	**OR**	**Lower 95% CI**	**Upper 95% CI**	***P***	**HR**	**Lower 95% CI**	**Upper 95% CI**	***P***	**HR**	**Lower 95% CI**	**Upper 95% CI**	***P***	**HR**	**Lower 95% CI**	**Upper 95% CI**	***P***
Clinical																		
BRCA mutation	*BRCA1*	*BRCA2*	0.20	0.04	0.76	.0271	1.63	0.73	3.63	.2298	2.20	0.96	5.04	.0627	3.50	1.36	9.02	.0094
Gleason sum at diagnosis	6-7	8-10	1.14	0.43	3.13	.7915	0.93	0.51	1.68	.8137	1.08	0.60	1.94	.7981	0.97	0.48	1.96	.9238
Age at start of therapy, years	Continuous		1.00	0.95	1.05	.8882	1.02	0.99	1.05	.2966	1.00	0.97	1.03	.8457	0.99	0.95	1.02	.4644
Baseline PSA, ng/mL	Continuous		1.00	1.00	1.00	.4079	1.00	1.00	1.00	.5325	1.00	1.00	1.00	.5434	1.00	1.00	1.00	.0959
T stage at diagnosis	T3-T4	T1-T2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
N stage at diagnosis	N1	N0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
M stage at diagnosis	M1	M0	1.53	0.65	3.71	.3358	1.03	0.61	1.73	.9213	0.74	0.44	1.27	.2739	0.77	0.41	1.43	.4024
Prior enzalutamide or abiraterone	Yes	No	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Prior docetaxel or cabazitaxel	Yes	No	0.67	0.30	1.47	.3220	1.48	0.90	2.43	.1188	1.66	1.02	2.71	.0432	2.53	1.34	4.79	.0042
Presence of bone metastases	Yes	No	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Presence of visceral metastases	Yes	No	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Presence of nodal metastases	Yes	No	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Molecular																		
BRCA mutation	*BRCA1*	*BRCA2*	0.22	0.05	0.86	.0389	1.40	0.59	3.31	.4416	2.20	0.97	4.96	.0586	2.61	1.07	6.39	.0356
Origin of mutation	Somatic	Germline	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Allelic status of mutation	Biallelic	Monoallelic	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Homozygous deletion *v* rest	Homozygous deletion	Rest	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Frameshift mutation *v* rest	Frameshift mutation	Rest	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Missense mutation *v* rest	Missense mutation	Rest	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

(Continued on following page)

TABLE 2. Multivariable Analyses for PSA_{50} Response, PSA-PFS, PFS, and OS (Continued)

			Multivariable Analysis of PSA_{50} Response				Multivariable Analysis of PSA-PFS				Multivariable Analysis of PFS				Multivariable Analysis of OS			
Name	**Levels**	**Reference**	**OR**	**Lower 95% CI**	**Upper 95% CI**	***P***	**HR**	**Lower 95% CI**	**Upper 95% CI**	***P***	**HR**	**Lower 95% CI**	**Upper 95% CI**	***P***	**HR**	**Lower 95% CI**	**Upper 95% CI**	***P***
Concurrent *TP53* mutation	Yes	No	0.51	0.22	1.19	.1204	2.82	1.70	4.68	.0001	1.79	1.11	2.89	.0167	2.26	1.27	4.05	.0058
Concurrent *PTEN* mutation	Yes	No	0.85	0.31	2.43	.7609	1.17	0.68	2.01	.5669	1.17	0.68	2.01	.5712	1.44	0.77	2.70	.2588
Concurrent *RB1* mutation	Yes	No	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Concurrent *SPOP* mutation	Yes	No	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Concurrent *AR* mutation	Yes	No	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Concurrent *TMPRSS2-ERG* fusion	Yes	No	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Abbreviations: HR, hazard ratio; M, metastasis; N, node; NA, not available; OR, odds ratio; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen; T, tumor.

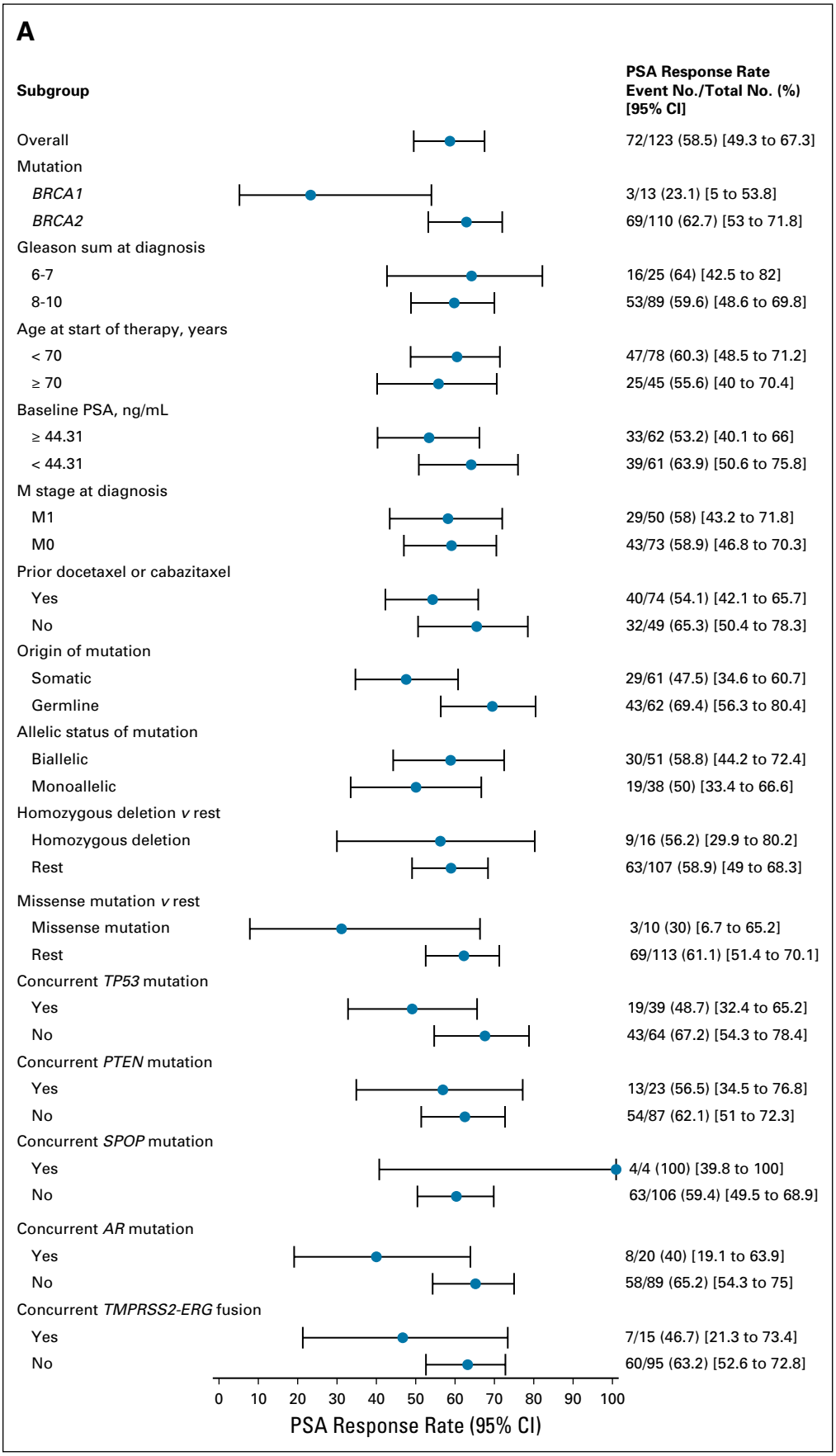


FIG 3. Forest plot analysis of clinical and molecular factors influencing efficacy outcomes. (A) Variables influencing PSA (> 50%) response rates. (B) Variables influencing PSA-PFS. (C) Variables influencing PFS. (D) Variables influencing OS. M, metastasis; N, node, NR, not reached; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen; T, tumor.

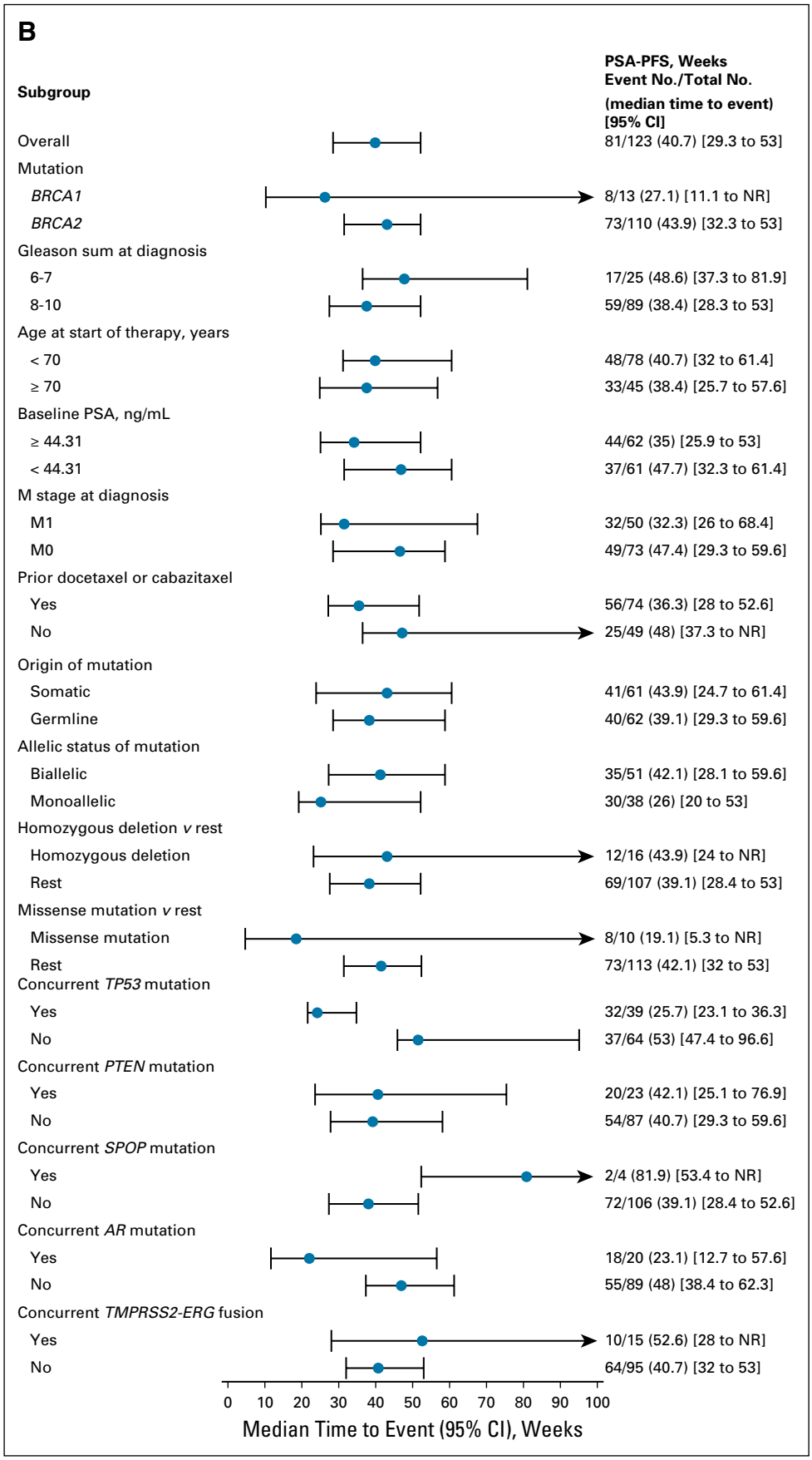


FIG 3. (Continued).

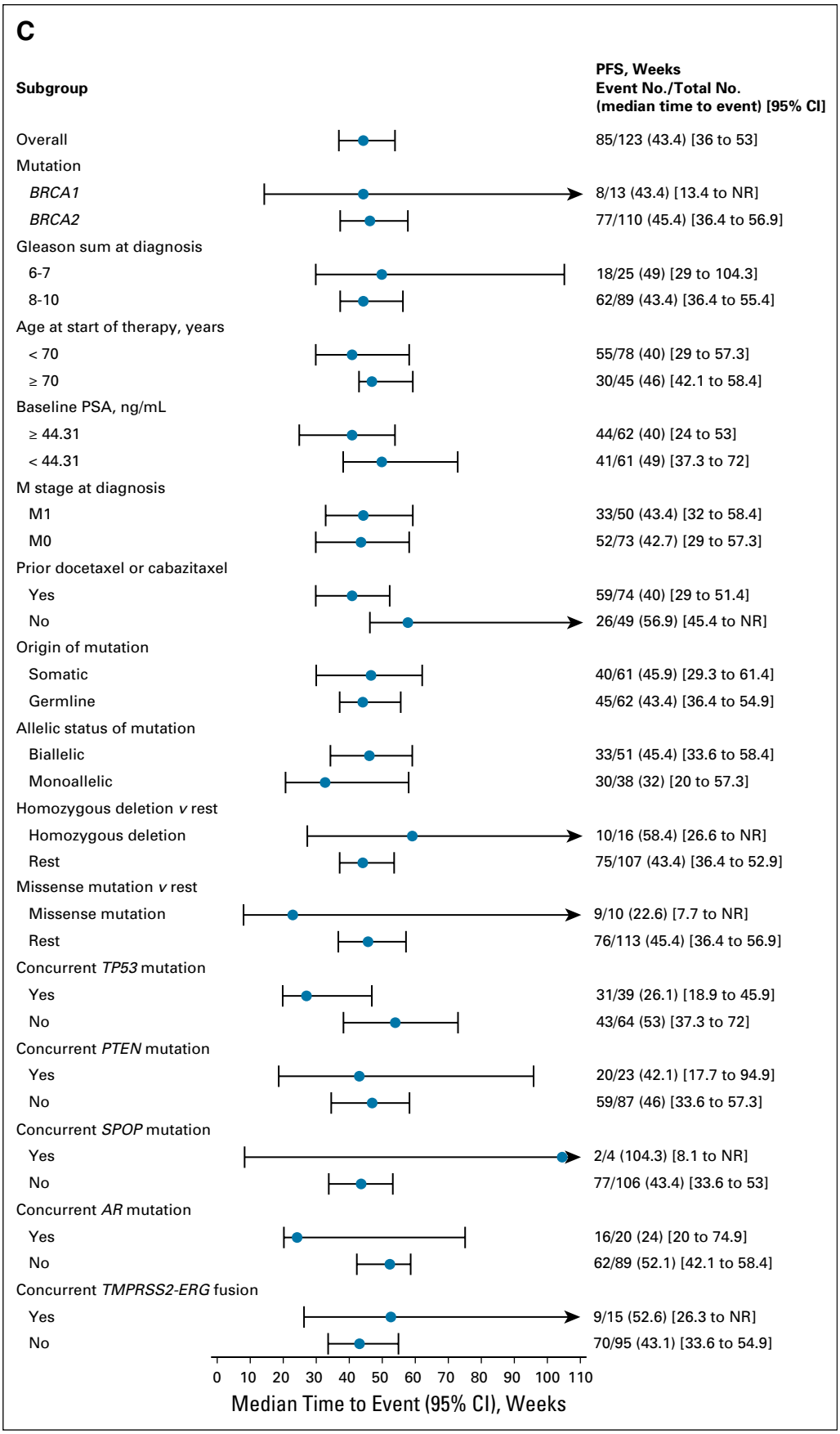


FIG 3. (Continued).

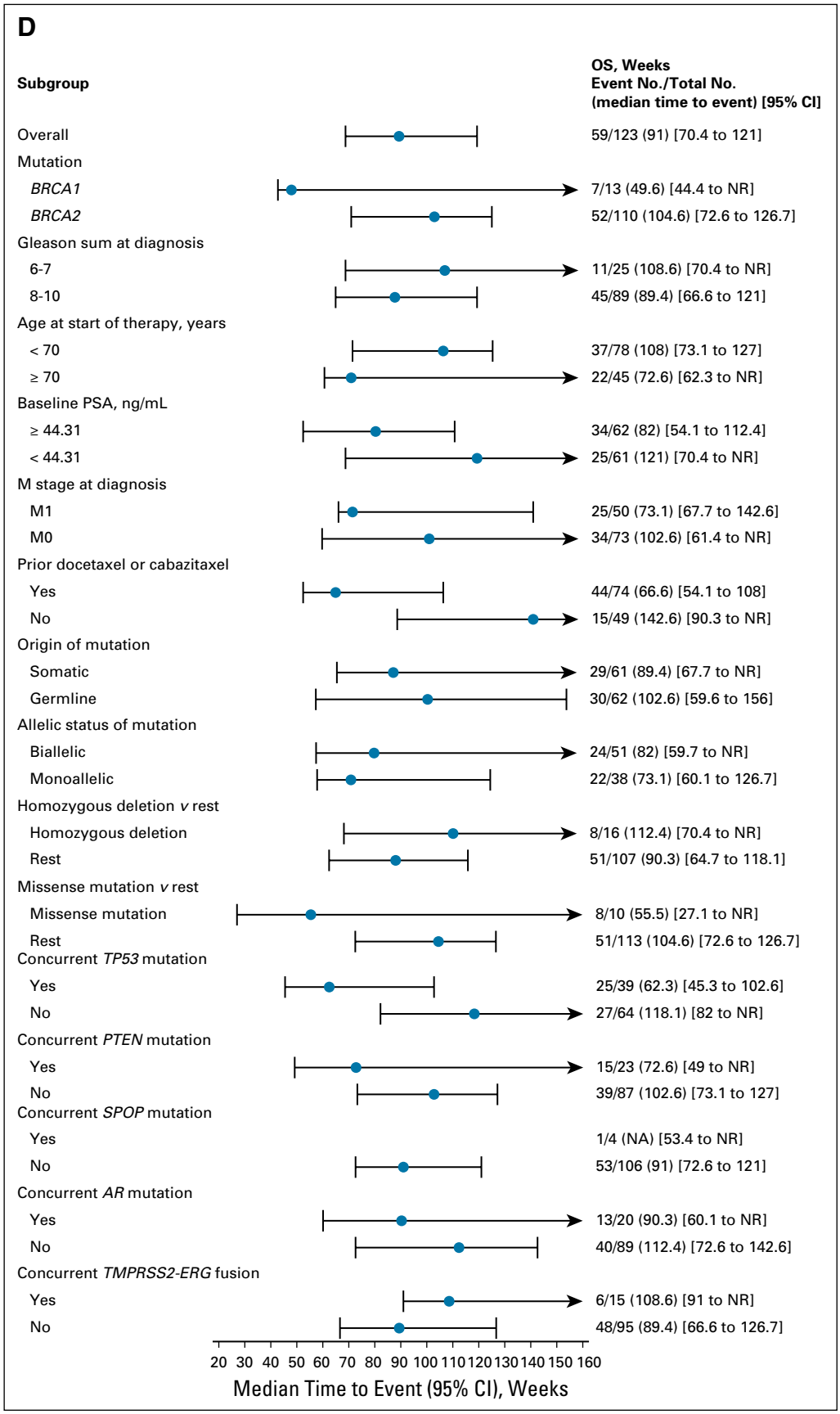


FIG 3. (Continued).

included in Appendix Tables A2 and A3. PSA-PFS was shorter in *BRCA1* patients compared with *BRCA2* patients (median 20 *v* 44 weeks; HR, 1.7; 95% CI, 0.4 to 7.3; *P* = .4). PFS was also shorter in *BRCA1* compared with *BRCA2* patients (median 40 *v* 60 weeks; HR, 2.1; 95% CI, 0.5 to 8.9; *P* = .3).

The median OS was 91.0 weeks (95% CI, 70.4 to 121) in the overall cohort. Again, OS was shorter in *BRCA1*- compared with *BRCA2*-altered patients (median 49.6 *v* 104.6 weeks; HR, 3.01; 95% CI, 1.32 to 6.83; *P* = .008; Fig 2D). This difference persisted after adjusting for age, Gleason sum, stage, baseline PSA, and previous taxane treatment (adjusted HR, 3.50; 95% CI, 1.36 to 9.02; *P* = .009) and after adjusting for concurrent *TP53* and *PTEN* mutations (adjusted HR, 2.61; 95% CI, 1.07 to 6.39; *P* = .04; Table 2). OS was numerically shorter in patients with somatic mutations, monoallelic mutations, missense mutations, and concurrent *TP53* alterations (Fig 3D).

DISCUSSION

The advent of the PARP inhibitors, olaparib and rucaparib, represents a major breakthrough in the management of advanced prostate cancer and heralds the beginning of the precision oncology era for this disease.[8] However, it is becoming apparent that not all mutated HRR genes display equivalent sensitivity to PARP inhibition in prostate cancer.[17,18] Previous studies have already suggested that mCRPC patients with germline or somatic non-*BRCA1/2* mutations have less favorable outcomes to a variety of PARP inhibitors compared with those with *BRCA1/2* alterations.[12,17,19] However, less attention has been given to examining the potential differential efficacy of PARP inhibitors in *BRCA1*-altered versus *BRCA2*-altered advanced prostate cancers (potentially because of the much lower relative prevalence of *BRCA1* in this disease), whereas preliminary evidence has suggested a possible blunting of PARP inhibitor sensitivity in the *BRCA1* subset.[20] Here, we aimed to formally examine this issue by forming a multicenter consortium to study and compare PARP inhibitor efficacy among *BRCA1*- versus *BRCA2*-associated prostate cancers.

We have found that the clinical activity of PARP inhibitors is diminished in mCRPC patients with germline or somatic *BRCA1* compared with *BRCA2* mutations. This decreased sensitivity did not appear to be driven by differences in baseline demographic or clinical characteristics in the two groups, and it persisted after adjusting for important clinical and genomic variables. Interestingly, when exploring the mutation characteristics of these *BRCA1/2*-altered patients, we observed generally improved clinical outcomes in those with biallelic (compared with monoallelic) mutations, but not in those with germline (compared with somatic) mutations. When considering *BRCA1/2* mutation mechanism, we observed broadly better clinical outcomes in patients with truncating (compared with missense) alterations, but not in those with homozygous deletions compared with other alterations. Finally, the presence of concurrent *TP53* mutations (which were observed in 55% and 36% of *BRCA1*- and *BRCA2*-altered cancers, respectively) were associated with numerically worse outcomes to PARP inhibitor treatment. In addition to the notion that *TP53* alterations broadly portend an overall worse prognosis in many cancer types, recent reports suggest that *TP53* mutations might be more permissive of the emergence of *BRCA1/2* reversion mutations (that restore the open reading frame) in *BRCA*-altered cancers that are exposed to PARP inhibitor treatment.[21,22] Such reversion mutations have been associated with secondary PARP inhibitor resistance in prostate and other *BRCA*-mutated cancers.

Interestingly, numerically better outcomes were observed in patients with concurrent *SPOP* mutations, although this represented a very small subset (4%) of the total population. The presence of *SPOP* mutations has also been associated with improved outcomes to a number of hormonal therapies as well.[23,24] In addition, studies have shown that *SPOP* mutations may increase genomic instability, potentially explaining the higher PARP inhibitor sensitivity in these cancers.[25] These hypothesis-generating findings require further validation.

Why might patients with *BRCA1*-altered mCRPC respond less favorably to PARP inhibitor treatment than *BRCA2*-altered patients? Our current data, taken together with previous findings, do not support the idea that there are differences in mutational origins (germline *v* somatic) when comparing *BRCA1*- and *BRCA2*-related cancers; the two genes are affected by germline alterations at equal frequencies.[14,21] Nor are there experimental or clinical data to support the notion that biallelic *BRCA1* inactivation in prostate cancer is associated with less HRR deficiency (and hence less synthetic lethality with PARP inhibition)[6] than biallelic *BRCA2* inactivation; in fact, HRR function might be impaired more significantly from *BRCA1* deficiency.[14,21] Therefore, one might predict that patients with mCRPC harboring biallelic *BRCA1* or *BRCA2* mutations would respond equally to PARP inhibitor treatment. However, our data and those of other investigators suggest that biallelic mutations are less common in *BRCA1*- compared with *BRCA2*-associated prostate cancers[11,14,26]; this appears to be one of the key differences potentially driving better responses to PARP inhibitors among the latter. Interestingly, after adjusting for zygosity status, there were no differences in outcomes among patients with biallelic *BRCA1*- versus *BRCA2*-mutated mCRPC (HR for PFS: 0.85, 95% CI, 0.20 to 3.60, *P* = .29; HR for OS: 1.80, 95% CI, 0.41 to 7.87, *P* = .77). Notably, a recent pan-cancer analysis of *BRCA1/2*-mutated cancers also suggested a greater amount of genome-wide loss of heterozygosity among cancers with biallelic versus monoallelic mutations, predicting enhanced PARP inhibitor sensitivity.[14] Finally,

another important observation (that has also been confirmed in other studies) is the greater coexistence of *TP53* mutations in *BRCA1*- versus *BRCA2*-mutated cancers[11,20]; the presence of concurrent *TP53* mutations may blunt PARP inhibitor efficacy in prostate cancer and possibly other cancers. Notably, after adjusting for *TP53* status, there were no differences in outcomes among patients with *BRCA1*- versus *BRCA2*-mutated mCRPC (HR for PFS: 1.22, 95% CI, 0.36 to 4.13, $P = .20$; HR for OS: 1.75, 95% CI, 0.51 to 6.02, $P = .25$).

This study had not only some strengths but also several limitations. The main shortcoming was that a variety of germline and somatic DNA sequencing platforms were used for the interrogation of *BRCA1/2* mutations. Furthermore, the tissue types used for tumor mutation analyses varied (sometimes involving archival primary tumor tissue, sometimes involving metastatic biopsies, and sometimes relying on ctDNA samples). Although the use of archival tissues is not likely to significantly alter the prevalence of *BRCA1/2* (or *SPOP* or *TMPRSS2-ERG*) mutations, which are generally thought to be truncal events,[27,28] archival samples would certainly underestimate the true prevalence of *PTEN*, *RB1*, and *AR* mutations.[29] However, the strict definition of *BRCA1/2* pathogenicity was a strength of our study, minimizing the inclusion of patients with variants of unknown significance alterations in this analysis. In addition, because of the inclusion of patients from 12 centers, it was not possible to centrally adjudicate clinical or radiographic progression events, and we relied on investigators' assessment of these end points in this retrospective study. We were also not able to harmonize the frequency of PSA assessments or radiographic assessments across the 12 sites. Thus, the most reliable clinical end point in this study is OS, whereas PSA-PFS and PFS estimates should be interpreted with caution. Some strengths of this study include the prospective determination of the sample size, the relatively large number of *BRCA1/2*-altered patients included (eg, larger than the PARP inhibitor–treated *BRCA1/2* populations in either the PROfound or TRITON2 studies), and the collection and annotation of additional molecular data allowing us to formulate hypotheses to explain the observed clinical differences.

In conclusion, to our knowledge, this is the first dedicated study to examine the potential differential effect of PARP inhibitor efficacy in *BRCA1*- versus *BRCA2*-associated prostate cancers. We show that PARP inhibitor activity is attenuated in mCRPC patients with *BRCA1* mutations and that sensitivity is highest in those with *BRCA2* mutations. The diminished efficacy among *BRCA1*-altered patients is not due to differences in mutation origin (germline *v* somatic) but rather appears to be associated with a greater number of monoallelic (rather than biallelic) mutations and a higher prevalence of concurrent *TP53* alterations in the *BRCA1* group. Thus, additional treatment options are needed for patients with *BRCA1*-altered mCRPC. These findings may have broad implications for other *BRCA1/2*-associated malignancies (breast, ovarian, and pancreatic cancers) where PARP inhibitors are used.

AFFILIATIONS

[1]Johns Hopkins University School of Medicine, Baltimore, MD
[2]Medstar Health Georgetown University, Baltimore, MD
[3]Indiana University School of Medicine, Indianapolis, IN
[4]University of Washington and Fred Hutch Cancer Research Center Seattle, Washington, DC
[5]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT
[6]Mayo Clinic, Scottsdale, AZ
[7]Tulane University School of Medicine, New Orleans, LA
[8]Oncology Center, Hospital Sírio-Libanês, São Paulo, Brazil
[9]Hospital Israelita Albert Einstein, São Paulo, Brazil
[10]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA
[11]University of California San Francisco, San Francisco, CA
[12]Englander Institute for Precision Medicine, Weill Cornell Medicine, New York, NY
[13]University of Michigan, Ann Arbor, MI

CORRESPONDING AUTHOR

Emmanuel S. Antonarakis, MD, Departments of Oncology and Urology, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, 201 N. Broadway, Room 9129, Baltimore, MD 21287; e-mail: eantona1@jhmi.edu.

SUPPORT

Supported by National Cancer Institute (NCI) SPORE Grant No. CA097186, Grant No. P30 CA015704, Congressional Designated Medical Research Program (CDMRP) Grant No. W81XWH-17-2-0043 all to H.H.C.

AUTHOR CONTRIBUTIONS

Conception and design: Fadi Taza, Costantine Albany, Neeraj Agarwal, A. Oliver Sartor, Cora N. Sternberg, Catherine H. Marshall, Emmanuel S. Antonarakis
Administrative support: Fadi Taza, Emmanuel S. Antonarakis
Provision of study materials or patients: Fadi Taza, Heather H. Cheng, Neeraj Agarwal, Alan Bryce, A. Oliver Sartor, Oren Smaletz, Mary-Ellen Taplin, Cora N. Sternberg, Panagiotis J. Vlachostergios, Ajjai S. Alva, Emmanuel S. Antonarakis
Collection and assembly of data: Fadi Taza, Albert E. Holler, Nabil Adra, Costantine Albany, Ryan Ashkar, Heather H. Cheng, Alexandra O. Sokolova, Neeraj Agarwal, Adam Kessel, Alan Bryce, Nellie Nafissi, A. Oliver Sartor, Diogo Bastos, Oren Smaletz, Jacob E. Berchuck, Mary-Ellen Taplin, Rahul Aggarwal, Cora N. Sternberg, Panagiotis J. Vlachostergios, Ajjai S. Alva, Catherine H. Marshall, Emmanuel S. Antonarakis
Data analysis and interpretation: Fadi Taza, Albert E. Holler, Wei Fu, Hao Wang, Nabil Adra, Costantine Albany, Alexandra O. Sokolova, Neeraj Agarwal, Alan Bryce, Pedro Barata, A. Oliver Sartor, Diogo Bastos, Mary-Ellen Taplin, Cora N. Sternberg, Ajjai S. Alva, Christopher Su, Catherine H. Marshall, Emmanuel S. Antonarakis
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by the authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/po/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Albert E. Holler

Stock and Other Ownership Interests: CareDX

Nabil Adra

Consulting or Advisory Role: Astellas Pharma, Bristol Myers Squibb Foundation, Merck
Research Funding: Merck, Genentech, Exelixis

Costantine Albany

Stock and Other Ownership Interests: Advaxis
Honoraria: Sanofi, AstraZeneca, Seattle Genetics
Consulting or Advisory Role: Seattle Genetics, AstraZeneca/MedImmune
Speakers' Bureau: Sanofi
Research Funding: Astex Pharmaceuticals, Merck, Bristol Myers Squibb, Lilly, Bayer
Travel, Accommodations, Expenses: Sanofi

Heather H. Cheng

Consulting or Advisory Role: AstraZeneca
Research Funding: Sanofi, Janssen, Clovis Oncology, Color Genomics Foundation, Fred Hutchinson Cancer Research Center

Neeraj Agarwal

Consulting or Advisory Role: Pfizer, Medivation/Astellas, Bristol Myers Squibb, AstraZeneca, Nektar, Lilly, Bayer, Pharmacyclics, Foundation Medicine, Astellas Pharma, Exelixis, Pfizer, Merck, Novartis, Eisai, Seattle Genetics, EMD Serono, Janssen Oncology, AVEO, Calithera Biosciences, MEI Pharma, Genentech, Gilead Sciences
Research Funding: Bayer, Bristol Myers Squibb, Takeda, Pfizer, Exelixis, Amgen, AstraZeneca, Calithera Biosciences, Celldex, Eisai, Genentech, Immunomedics, Janssen, Merck, Lilly, Nektar, ORIC Pharmaceuticals, CRISPR therapeutics, Arvinas

Alan Bryce

Honoraria: Astellas Pharma, Bayer
Travel, Accommodations, Expenses: Clovis Oncology, Phosplatin Therapeutics

Pedro Barata

Consulting or Advisory Role: Bayer, Bristol Myers Squibb, Pfizer, EMD Serono, Eisai, Caris Life Sciences, Clovis Oncology, Dendreon
Research Funding: Blue Earth Diagnostics

A. Oliver Sartor

Stock and Other Ownership Interests: Lilly, GlaxoSmithKline, AbbVie, Cardinal Health, United Health Group, PSMA Therapeutics, Clarity Pharmaceuticals, Noria Therapeutics, Clovis Oncology
Consulting or Advisory Role: Bayer, Sanofi, AstraZeneca, Dendreon , Constellation Pharmaceuticals, Advanced Accelerator Applications, Pfizer, Bristol Myers Squibb, Bavarian Nordic, EMD Serono, Astellas Pharma, Progenics, Blue Earth Diagnostics, Myovant Sciences, Myriad Genetics, Novartis, Clarity Pharmaceuticals, Fusion Pharmaceuticals, Isotopen Technologien, Janssen, Noxopharm, Clovis Oncology, Noria Therapeutics, Point Biopharma, TeneoBio, Telix Pharmaceuticals, Theragnostics
Research Funding: Bayer, Sanofi, Endocyte, Merck, InVitae, Constellation Pharmaceuticals, Advanced Accelerator Applications, AstraZeneca, Dendreon, SOTIO, Janssen, Progenics
Expert Testimony: Sanofi
Travel, Accommodations, Expenses: Bayer, Johnson & Johnson, Sanofi, AstraZeneca, Progenics

Diogo Bastos

Honoraria: MSD, Roche, Bristol Myers Squibb, Janssen-Cilag, Astellas Pharma, AstraZeneca, Bayer
Consulting or Advisory Role: Roche, Bayer, Janssen-Cilag, MSD Oncology
Research Funding: Janssen-Cilag, Pfizer, Astellas Pharma
Travel, Accommodations, Expenses: Janssen-Cilag, Bayer

Oren Smaletz

Stock and Other Ownership Interests: AstraZeneca, GlaxoSmithKline, Novartis, Roche, Sanofi
Honoraria: AstraZeneca, Astellas Pharma
Consulting or Advisory Role: Astellas Pharma, Pfizer, Ipsen, Lilly, Janssen
Research Funding: Janssen, Bristol Myers Squibb
Travel, Accommodations, Expenses: Bristol Myers Squibb, Ipsen

Jacob E. Berchuck

Employment: Cityblock Health
Stock and Other Ownership Interests: Genome Medical, Cityblock Health
Consulting or Advisory Role: Genome Medical
Patents, Royalties, Other Intellectual Property: Institutional patent filed on methods for detecting prostate cancer resistance using cell-free DNA

Mary-Ellen Taplin

Honoraria: Janssen-Ortho, Clovis Oncology, Astellas Pharma, Incyte, UpToDate, Research to Practice, Pfizer, Bayer, Amgen, AstraZeneca, Progenics, Guidepoint Global, Celgene, Merck, GlaxoSmithKline, Myovant Sciences, Roivant, AbbVie, Arcus Biosciences, Constellation Pharmaceuticals
Consulting or Advisory Role: Janssen-Ortho, Bayer, Guidepoint Global, Best Doctors Inc, UpToDate, Clovis Oncology, Research to Practice, Myovant Sciences, Incyte, Pfizer, AstraZeneca, Arcus Ventures
Research Funding: Janssen-Ortho, Medivation, Bayer, Pfizer
Travel, Accommodations, Expenses: Medivation, Janssen Oncology, Tokai Pharmaceuticals, Astellas Pharma, Incyte, Pfizer, Clovis Oncology, Bayer

Rahul Aggarwal

Honoraria: Clovis Oncology
Consulting or Advisory Role: AstraZeneca, Dendreon, Advanced Accelerator Applications, Clovis Oncology, Axiom Biotechnologies
Research Funding: Zenith Epigenetics, Novartis, Xynomic Pharma, Cancer Targeted Technology, Janssen, Merck, AbbVie, Amgen, AstraZeneca, BioXcel Therapeutics

Cora N. Sternberg

Consulting or Advisory Role: Bayer, MSD, Pfizer, Roche, Incyte, AstraZeneca, Merck, Medscape, UroToday, Astellas Pharma, Genzyme, Immunomedics, Foundation Medicine

Ajjai S. Alva

Consulting or Advisory Role: AstraZeneca, Merck, Pfizer, Bristol Myers Squibb
Research Funding: Genentech, Bristol Myers Squibb, Merck Sharp & Dohme, Prometheus, Mirati Therapeutics, AstraZeneca, Roche, Bayer, Progenics, Astellas Pharma, Arcus Biosciences, Harpoon Therapeutics, Celgene, Janssen
Travel, Accommodations, Expenses: Merck, Bristol Myers Squibb

Catherine H. Marshall

Consulting or Advisory Role: McGraw-Hill Education, Dendreon, Bayer
Research Funding: Conquer Cancer Foundation/Bristol Myers Squibb
Travel, Accommodations, Expenses: Dava Oncology, Bayer

Emmanuel S. Antonarakis

Honoraria: Sanofi, Dendreon, Medivation, Janssen Biotech, ESSA, Astellas Pharma, Merck, AstraZeneca, Clovis Oncology
Consulting or Advisory Role: Sanofi, Dendreon, Janssen Biotech, ESSA, Merck, AstraZeneca, Clovis Oncology, Lilly, Bayer
Research Funding: Janssen Biotech, Johnson & Johnson, Sanofi, Dendreon, Aragon Pharmaceuticals, Exelixis, Millennium, Genentech, Novartis, Astellas Pharma, Tokai Pharmaceuticals, Merck, AstraZeneca, Clovis Oncology, Constellation Pharmaceuticals
Patents, Royalties, Other Intellectual Property: Coinventor of a biomarker technology that has been licensed to Qiagen
Travel, Accommodations, Expenses: Sanofi, Dendreon, Medivation

No other potential conflicts of interest were reported.

REFERENCES

1. Gillessen S, Attard G, Beer TM, et al: Management of patients with advanced prostate cancer: Report of the advanced prostate cancer Consensus Conference 2019. Eur Urol 77:508-547, 2020
2. Pritchard CC, Mateo J, Walsh MF, et al: Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med 375:443-453, 2016
3. Chung JH, Dewal N, Sokol E, et al: Prospective comprehensive genomic profiling of primary and metastatic prostate tumors. JCO Precis Oncol 3:1-23, 2019
4. Castro E, Romero-Laorden N, del Pozo A, et al: PROREPAIR-B: A prospective cohort study of the impact of germline DNA repair mutations on the outcomes of patients with metastatic castration-resistant prostate cancer. J Clin Oncol 37:490-503, 2019
5. Annala M, Vandekerkhove G, Khalaf D, et al: Circulating tumor DNA genomics correlate with resistance to abiraterone and enzalutamide in prostate cancer. Cancer Discov 8:444-457, 2018
6. Farmer H, McCabe N, Lord CJ, et al: Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 434:917-921, 2005
7. Dhawan M, Ryan CJ, Ashworth A: DNA repair deficiency is common in advanced prostate cancer: New therapeutic opportunities. Oncologist 21:940-945, 2016
8. Antonarakis ES, Gomella LG, Petrylak DP: When and how to use PARP inhibitors in prostate cancer: A systematic review of the literature with an update on ongoing trials. Eur Urol Oncol 3:594-611, 2020
9. Hussain M, Mateo J, Fizazi K, et al: Survival with olaparib in metastatic castration-resistant prostate cancer. N Engl J Med 383:2345-2357, 2020
10. de Bono J, Mateo J, Fizazi K, et al: Olaparib for metastatic castration-resistant prostate cancer. N Engl J Med 382:2091-2102, 2020
11. Abida W, Patnaik A, Campbell D, et al: Rucaparib in men with metastatic castration-resistant prostate cancer harboring a BRCA1 or BRCA2 gene alteration. J Clin Oncol 38:3763-3772, 2020
12. Abida W, Campbell D, Patnaik A, et al: Non-BRCA DNA damage repair gene alterations and response to the PARP inhibitor rucaparib in metastatic castration-resistant prostate cancer: Analysis from the phase II TRITON2 study. Clin Cancer Res 26:2487-2496, 2020
13. Scher HI, Morris MJ, Stadler WM, et al: Trial design and objectives for castration-resistant prostate cancer: Updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol 34:1402-1418, 2016
14. Sokol ES, Pavlick D, Khiabanian H, et al: Pan-cancer analysis of BRCA1 and BRCA2 genomic alterations and their association with genomic instability as measured by genome-wide loss of heterozygosity. JCO Precis Oncol 4:442-465, 2020
15. Abida W, Cyrta J, Heller G, et al: Genomic correlates of clinical outcome in advanced prostate cancer. Proc Natl Acad Sci 116:11428-11436, 2019
16. cBioPortal for Cancer Genomics Database: www.cbioportal.org
17. Marshall CH, Sokolova AO, McNatty AL, et al: Differential response to olaparib treatment among men with metastatic castration-resistant prostate cancer harboring BRCA1 or BRCA2 versus ATM mutations. Eur Urol 76:452-458, 2019
18. Luo J, Antonarakis ES: PARP inhibition—Not all gene mutations are created equal. Nat Rev Urol 16:4-6, 2019
19. Antonarakis ES: Olaparib for DNA repair-deficient prostate cancer—One for all, or all for one? Nat Rev Clin Oncol 17:455-456, 2020
20. Markowski MC, Antonarakis ES: BRCA1 versus BRCA2 and PARP inhibitor sensitivity in prostate cancer: More different than alike? J Clin Oncol 38:3735-3739, 2020
21. Jonsson P, Bandlamudi C, Cheng ML, et al: Tumour lineage shapes BRCA-mediated phenotypes. Nature 571:576-579, 2019
22. Pettitt SJ, Frankum JR, Punta M, et al: Clinical BRCA1/2 reversion analysis Identifies hotspot mutations and predicted neoantigens associated with therapy resistance. Cancer Discov 10:1475-1488, 2020
23. Boysen G, Rodrigues DN, Rescigno P, et al: SPOP-mutated/CHD1-deleted lethal prostate cancer and abiraterone sensitivity. Clin Cancer Res 24:5585-5593, 2018
24. Swami U, Isaacsson Velho P, Nussenzveig R, et al: Association of SPOP mutations with outcomes in men with de novo metastatic castration-sensitive prostate cancer. Eur Urol 78:652-656, 2020
25. Shenoy TR, Boysen G, Wang MY, et al: CHD1 loss sensitizes prostate cancer to DNA damaging therapy by promoting error-prone double-strand break repair. Ann Oncol 28:1495-1507, 2017
26. Hughley R, Karlic R, Joshi H, et al: Etiologic index—A case-only measure of BRCA1/2—Associated cancer risk. N Engl J Med 383:286-288, 2020
27. Abida W, Armenia J, Gopalan A, et al: Prospective genomic profiling of prostate cancer across disease states reveals germline and somatic alterations that may affect clinical decision making. JCO Precis Oncol 2017:1-16, 2017
28. Mateo J, Seed G, Bertan C, et al: Genomics of lethal prostate cancer at diagnosis and castration resistance. J Clin Invest 130:1743-1751, 2020
29. Armenia J, Wankowicz SAM, Liu D, et al: The long tail of oncogenic drivers in prostate cancer. Nat Genet 50:645-651, 2018

APPENDIX

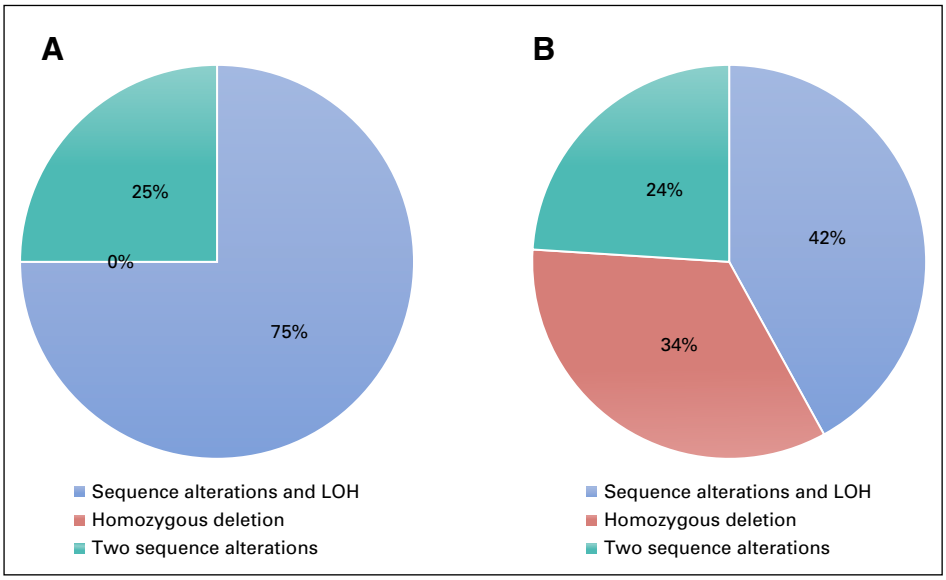


FIG A1. Pie charts of the biallelic inactivation mechanisms by *BRCA* mutation type: (A) *BRCA1* and (B) *BRCA2*. LOH, loss of heterozygosity.

TABLE A1. Biallelic Inactivation Mechanisms, by *BRCA* Mutation Type

Biallelic Inactivation Mechanism	Overall, No. (%)	*BRCA1*, No. (%)	*BRCA2*, No. (%)	*P*
No. of patients	51	4 (8)	47 (92)	
Sequence alteration plus LOH				.20
No	28 (55)	1 (25)	27 (58)	
Yes	23 (45)	3 (75)	20 (42)	
Homozygous deletion				.15
No	35 (69)	4 (100)	31 (66)	
Yes	16 (31)	0 (0)	16 (34)	
Two sequence alterations				.90
No	39 (76)	3 (75)	36 (76)	
Yes	12 (24)	1 (25)	11 (24)	

Abbreviation: LOH, loss of heterozygosity.

TABLE A2. Baseline Demographic, Clinical, and Genomic Data Overall and by Mutation Type, in the *BRCA1*-Responding and Nonresponding Patients

Characteristic	Overall Patients, No. (%)	*BRCA1* Responders, No. (%)	*BRCA1* Nonresponders, No. (%)
No. of patients	13	3	10
Gleason sum at diagnosis			
8-10	10 (77)	3 (100)	7 (70)
6-7	0		
Unknown	3 (23)	0	3 (30)
Age at start of therapy, years			
Median/mean	71/69	71/72	67/69
Baseline PSA, ng/mL	123	13	110
Median/mean	47/172	241/589	24/47
Min-max	0-1,459	68-1,459	0-143
T stage at diagnosis			
T1-T2	3 (23)	0 (0)	3 (30)
T3-T4	10 (77)	3 (100)	7 (70)
N stage at diagnosis			
N0	5 (38)	2 (66)	3 (30)
N1	8 (62)	1 (34)	7 (70)
M stage at diagnosis			
M0	2 (15)	1 (34)	1 (10)
M1	11 (85)	2 (66)	9 (90)
Prior docetaxel or cabazitaxel			
No	3 (23)	0 (0)	3 (30)
Yes	10 (77)	3 (100)	7 (70)
Prior enzalutamide or abiraterone			
No	1 (7)	0 (0)	1 (10)
Yes	12 (93)	3 (100)	9 (90)
Presence of bone metastases			
No	1 (7)	0 (0)	1 (10)
Yes	12 (93)	3 (100)	9 (90)
Presence of visceral metastases			
No	10 (77)	2 (66)	8 (80)
Yes	3 (23)	1 (34)	2 (20)
Presence of nodal metastases			
No	6 (55)	1 (34)	5 (50)
Yes	7 (45)	2 (66)	5 (50)
Origin of mutation			
Germline	6 (55)	2 (66)	4 (40)
Somatic	7 (45)	1 (34)	6 (60)
Allelic status of mutation	9	3	6
Monoallelic	5 (50)	2 (66)	3 (42)
Biallelic	4 (50)	1 (34)	3 (58)
Mutation mechanism			
Frameshift	3 (25)	0 (0)	3 (30)
Homozygous deletion	0 (0)	0 (0)	0 (0)
Missense	4 (30)	0 (0)	4 (40)

(Continued on following page)

TABLE A2. Baseline Demographic, Clinical, and Genomic Data Overall and by Mutation Type, in the *BRCA1*-Responding and Nonresponding Patients (Continued)

Characteristic	Overall Patients, No. (%)	*BRCA1* Responders, No. (%)	*BRCA1* Nonresponders, No. (%)
Nonsense	3 (23)	1 (33)	2 (20)
Rearrangement	2 (15)	1 (33)	1 (1)
Splicing	1 (7)	1 (33)	0 (0)
Concurrent *TP53* mutation	11		
No	5 (45)	1 (34)	4 (50)
Yes	6 (55)	2 (66)	4 (50)
Concurrent *PTEN* mutation	11		
No	10 (90)	3 (100)	7 (88)
Yes	1 (10)	0 (0)	1 (12)
Concurrent *RB1* mutation	11		
No	11 (100)	3 (100)	8 (100)
Yes	0 (0)	0 (0)	0 (0)
Concurrent *SPOP* mutation	11		
No	11 (100)	3 (100)	8 (100)
Yes	0	0	0
Concurrent *AR* mutation	11		
No	10 (90)	3 (100)	7 (88)
Yes	1 (10)	0	1 (12)

Abbreviations: M, metastasis; N, node; PSA, prostate-specific antigen; T, tumor.

TABLE A3. Baseline Demographic, Clinical, and Genomic Data Overall and by Mutation Type, in the *BRCA2*-Responding and Nonresponding Patients

Characteristic	Overall Patients, No. (%)	*BRCA2* Responders, No. (%)	*BRCA2* Nonresponders, No. (%)
No. of patients	110	69	41
Gleason sum at diagnosis			
8-10	10 (77)	49 (71)	30 (73)
6-7	0	16 (23)	9 (22)
Unknown	3 (23)	4 (6)	2 (5)
Age at start of therapy, years			
Median/mean	71/69	66/65	67/65
Baseline PSA, ng/mL			
Median/mean	47/172	35/310	54/266
Min-max	0-1,459	0.04-6,394	0.07-2,026
T stage at diagnosis			
T1-T2	28 (25)	18 (26)	10 (25)
T3-T4	82 (75)	51 (74)	31 (75)
N stage at diagnosis			
N0	73 (66)	49 (63)	24 (58)
N1	37 (34)	20 (37)	17 (42)
M stage at diagnosis			
M0	52 (47)	35 (50)	17 (41)
M1	58 (53)	34 (50)	24 (59)
Prior docetaxel or cabazitaxel			
No	46 (42)	32 (46)	14 (34)
Yes	64 (38)	37 (54)	27 (66)
Prior enzalutamide or abiraterone			
No	13 (12)	8 (11)	5 (11)
Yes	97 (88)	61 (89)	36 (89)
Presence of bone metastases			
No	19 (18)	14 (20)	5 (10)
Yes	91 (82)	55 (100)	36 (90)
Presence of visceral metastases			
No	10 (77)	54 (66)	28 (80)
Yes	3 (23)	15 (34)	13 (20)
Presence of nodal metastases			
No	65 (60)	42 (60)	23 (56)
Yes	45 (40)	27 (40)	18 (44)
Origin of mutation			
Germline	56 (50)	40 (58)	16 (39)
Somatic	54 (50)	29 (42)	25 (61)
Allelic status of mutation	80	47	33
Monoallelic	33 (41)	17 (36)	16 (48)
Biallelic	47 (59)	30 (64)	17 (52)
Mutation mechanism			
Frameshift	68 (62)	44 (64)	24 (60)
Homozygous deletion	16 (14)	10 (15)	6 (15)

(Continued on following page)

TABLE A3. Baseline Demographic, Clinical, and Genomic Data Overall and by Mutation Type, in the *BRCA2*-Responding and Nonresponding Patients (Continued)

Characteristic	Overall Patients, No. (%)	*BRCA2* Responders, No. (%)	*BRCA2* Nonresponders, No. (%)
Missense	6 (6)	3 (4)	3 (7)
Nonsense	9 (8)	7 (10)	2 (5)
Rearrangement	9 (8)	4 (6)	5 (12)
Splicing	2 (2)	1 (1)	1 (1)
Concurrent *TP53* mutation			
No	59 (64)	42 (71)	17 (50)
Yes	33 (36)	17 (29)	16 (50)
Concurrent *PTEN* mutation			
No	77 (77)	51 (80)	26 (75)
Yes	22 (23)	13 (20)	9 (25)
Concurrent *RB1* mutation			
No	80 (80)	53 (82)	27 (77)
Yes	19 (20)	11 (18)	8 (23)
Concurrent *SPOP* mutation			
No	95 (96)	60 (94)	35 (100)
Yes	4 (4)	4 (4)	0 (0)
Concurrent *AR* mutation			
No	79 (80)	54 (85)	25 (71)
Yes	19 (20)	9 (15)	10 (29)

Abbreviations: M, metastasis; N, node; PSA, prostate-specific antigen; T, tumor.

special articles

Adopting Consensus Terms for Testing in Precision Medicine

Nikki A. Martin, MA[1]; Joel E. Tepper, MD[2]; Veda N. Giri, MD[3]; Thomas E. Stinchcombe, MD[4]; Heather H. Cheng, MD, PhD[5,6,7]; Milind M. Javle, MD[8]; and Eric Q. Konnick, MD, MS[7,9]

abstract

PURPOSE Despite the well-understood benefits of biomarker and genetic testing in precision medicine, uptake remains low, particularly for patients with low socioeconomic status and minority ethnic backgrounds. Patients report having limited familiarity with testing terminology and may not be able to accurately explain testing's role in treatment decisions. Patient confusion and lack of understanding is exacerbated by a multiplicity of overlapping terms used in communicating about testing. A LUNGevity Foundation–led working group composed of five professional societies, 23 patient advocacy groups, and 19 industry members assessed and recommended specific terms for communicating with patients on testing for tumor characteristics and germline mutations.

METHODS Members completed a precision oncology testing framework analysis (biomarkers, germline variants, testing modalities, biospecimen, and commonly used testing terms) for nine solid tumors and blood cancers. The evaluation was segmented into terms that distinguish between somatic and germline testing. Additional data were captured in a comprehensive survey (1,650 respondents) led by FORCE (Facing Our Risk of Cancer Empowered) on patient preferences on germline testing terms.

RESULTS Thirty-three terms were noted in patient education related to biomarker, genetic, and genomic testing. Biomarker testing was selected as the preferred term for testing for somatic (acquired) alterations and other biomarkers. Genetic testing for an inherited mutation and genetic testing for inherited cancer risk were selected as the preferred terms for testing for germline variants.

CONCLUSION Democratizing comprehension about precision oncology testing through intentional use of plain language and common umbrella terminology by oncology health care providers and others in the oncology ecosystem may help improve understanding and communication, and facilitate shared decision making about the role of appropriate testing in treatment decisions and other aspects of oncology care.

JCO Precis Oncol 5:1563-1567. © 2021 by American Society of Clinical Oncology

Precision medicine has transformed the practice of oncology, offering opportunities for significantly improved outcomes in an array of solid and hematologic malignancies. Indeed, professional guidelines routinely recommend the application of genomic and laboratory techniques in oncology to both direct treatment and elucidate inherited cancer risks.

However, many eligible patients are not benefiting from advances in precision medicine because of low rates in both biomarker testing for tumor-specific therapies and genetic testing for inherited mutations that indicate increased cancer risk. In lung cancer, for example, a study of 5,688 patients with non–small-cell lung cancer from 2011 to 2016 demonstrated that 15.4% received broad-based genomic sequencing and 84.6% received single gene testing for *EGFR* and/or *ALK*.[1] A more recent study evaluating testing rates showed that only 7% of patients receiving care in community oncology settings received the recommended testing for all seven biomarkers specified in the active clinical guidelines.[2] Likewise, in patients with gastrointestinal stromal tumor, recent data indicate that fewer than 27% received recommended tumor testing for *KIT* mutations,[3] and only 40% of patients with colorectal cancer received recommended testing for known actionable mutations.[4] Testing according to current guidelines remains below 50% for most populations recommended for inherited cancer risk testing. This includes subgroups of patients with breast cancer, and patients with ovarian, pancreatic, and metastatic prostate cancer.[5]

There are multiple likely reasons for this pervasive undertesting, including limited availability of adequate samples, lack of provider knowledge or support (including testing and counseling resources), geographic factors, racial disparities, socioeconomic factors, limited

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on July 19, 2021 and published at ascopubs.org/journal/po on October 6, 2021: DOI https://doi.org/10.1200/PO.21.00027

CONTEXT

Key Objective

Advanced diagnostic cancer risk and oncology testing that informs personalized treatment decisions for patients has been challenging to communicate effectively because of medical jargon and overlapping terminology. For the first time, a multistakeholder pan-cancer working group analyzed the landscape of precision-medicine terminology and provided recommendations for plain language terms that providers and other stakeholders can use to address gaps in patient health literacy and improve shared decision making.

Knowledge Generated

Recommended consensus umbrella testing terms for patient communication were biomarker testing (for acquired tumor characteristics) and genetic testing for an inherited mutation and genetic testing for inherited cancer risk (for germline testing).

Relevance

A recently updated CDC definition of health literacy incorporates the role of organizations in making health information equitably accessible and understandable to patients. When used consistently, common cancer testing terminology can address poor patient comprehension of the role of testing in accurate treatment selection.

insurance coverage, and reimbursement challenges.[6] Studies suggest that demographic factors such as language, age, and insurance status may contribute to decreased access to germline genetic testing in prostate cancer.[7] In colorectal cancer, study findings suggest that socioeconomic status, insurance status, and hospital care settings could also play a role in access to biomarker testing.[8] Recent studies have shown lower biomarker testing rates in patients with cancer from underserved communities.[9,10] For example, a recent retrospective observational study of patients with non–small-cell lung cancer using the Flatiron Health database showed a more than 10 percentage point difference in White (50.1%) patients receiving biomarker testing with next-generation sequencing compared with Black patients (39.8%).[11] Inequitable access to testing and treatment is also exacerbated by inadequate inclusion of diverse ethnicities in the diagnostic test reference cohorts compared with populations of these patients receiving testing in the clinic. One study showed that the proportion of American Indian or Alaskan Native and Native Hawaiian or Other Pacific Islander in a pan-cancer institutional cohort receiving NGS testing was significantly lower than that of patients of European ancestry.[10]

Managing these complex challenges will require long-term policy, process, and infrastructure solutions, but there are also more immediate opportunities at hand to address a key driver of suboptimal testing rates: confusion and lack of understanding among patients and caregivers about the language used in precision medicine. Recent preliminary results (manuscript in preparation) from Cancer Support Community, a pan-cancer patient advocacy organization, found wide variability of familiarity of terms used in patient education about precision medicine. The research surveyed 30 patients and caregivers (21 women and nine men) with education levels ranging from high school to post-graduate school who have experience with malignancies such as breast cancer (eight), prostate cancer (six), lung cancer (three), and other cancers (13). Almost two thirds of patients with cancer and caregivers reported never having heard of or not knowing anything about the terms precision medicine (61%) and cancer subtype (66%). When asked about biomarker testing, which can also be called molecular testing, tumor profiling, somatic testing, or genomic testing of cancer cells, most patients and caregivers reported being familiar with the term and were able to articulate an accurate definition. However, although 73% indicated a basic understanding of targeted therapy, most respondents were unable to provide an accurate definition. Most respondents (90%) reported they understood the term genetic testing for inherited cancer risk and were able to articulate an accurate meaning (Table 1).

Additional data from a separate study (manuscript in preparation) by the patient advocacy group LUNGevity Foundation that surveyed patients with lung cancer about recognition of precision medicine terms found that awareness of the term targeted therapy has penetrated the patient population. When patients with lung cancer were asked whether they had heard the terms biomarker testing, mutation testing, genetic testing, genomic testing, tumor profiling, and molecular testing, 88% of patients responded that they had heard of at least one testing term. The somatic mutation testing term that had the highest level of familiarity to patients with lung cancer was biomarker testing, with 92% of patients in the LUNGevity network and 65% of patients who are unaffiliated with a patient advocacy group citing familiarity.

Patient-reported confusion about biomarker testing is likely driven, in part, by the lack of consistency and multitude of different terms used by providers, other experts, and

TABLE 1. Survey of 30 Cancer Patients' and Caregivers' Familiarity With Precision Medicine Terms

Concept	Never Heard of It (%)	Heard of But Do Not Know Anything About It (%)	Heard of and Self-Reported a Basic Understanding (%)
Precision medicine	32	29	39
Biomarker testing	3	30	67
Targeted therapy	7	20	73
Genetic testing for inherited cancer risk	0	10	90
Cancer subtype	53	13	33

commercial companies when discussing testing.[12] When asked, patients often cite difficulty sorting out complex information about what tests to have, what tests they may have had, how results can guide treatment and care decisions, and how test results may apply to patients accessing clinical trials. In a survey of 648 patients with breast cancer from diverse communities conducted by patient advocacy groups Facing Our Risk of Cancer Empowered (FORCE) and Living Beyond Breast Cancer, respondents seemed to understand germline genetic testing the most, and tumor biomarker testing for acquired alterations the least. Almost half of the respondents (46%) reported that they did not understand their tumor biomarker test results. In addition, some respondents expressed confusion about the difference between genetic testing for inherited mutations (pathogenic variants) and tumor testing for acquired mutations only found in the tumor.[13]

PROPOSAL

Although precision medicine and testing can be complicated subjects for a lay audience, it is important that the medical community and others communicating with patients strive for language that is both accurate and accessible so that our patients can be active partners in managing their care and engaging in shared decision making about their best care options.

To assess the extent of patient and caregiver confusion about testing terminology and propose potential remedies, over the last year, LUNGevity Foundation has convened a multistakeholder pan-cancer working group of patient advocacy organizations, professional societies, medical product developers, and laboratories.

After documenting more than 33 different terms related to biomarker, genetic, and genomic testing that are currently in use within oncology clinical care and patient education, the working group sought consensus among the stakeholders on several proposed preferred terms that could be applicable across tumor types.[14] These terms were evaluated by working group members, which included patient advocacy organizations with expertise in precision medicine for their disease space, professional societies such as the Association for Molecular Pathology, the Association of Community Cancer Centers, and the National Society of Genetic Counselors, and industry represented by pharma and biotech, laboratories, and test manufacturers. In addition, for the selection of the germline testing term, terms were refined based on feedback received through surveys of more than 1,700 patients and caregivers. Although working group members did not perform an additional patient survey for the selection of a term for testing for acquired somatic and nongenomic biomarkers, a subset of member organizations had previously queried their patient communities about terms under consideration, and these insights were integrated into the discussion and selection of a preferred term.

The result of this effort was the recommendation that all stakeholders in the oncology ecosystem adopt common, consistent terms for biomarker and germline genetic testing for all cancer types. Specifically, the working group proposed the following:

1. For tests that identify characteristics, targetable findings, or other test results originating from malignant tissue or blood, the recommended umbrella term is *biomarker testing.*
2. For tests that identify germline mutations or variants, the recommendation is for *genetic testing for an inherited mutation* and *genetic testing for inherited cancer risk*, which would be used in the appropriate specific clinical scenario.

These recommendations, which are detailed in a recently released White Paper,[15] are designed to be cross-cutting umbrella terms that can be used in all care settings, with the recognition that there will be important nuances relating to individual patients' specific disease states and family histories. It is expected that providers and others who communicate with patients will augment the baseline terms with necessary additional explanations, to ensure that patients receive accurate and appropriate information about their diagnosis, prognosis, and care options. It should be noted that providers who practice in diverse cross-cultural and multiracial communities where English is not the first language may benefit from additional adaptation of these terms for optimal provider-patient communication. Guiding principles for cultural adaptation include a four-step process: (1) forward translation; (2) expert panel review of the translated terms; (3) back-translation, and (4) testing the terms with the intended audience in interviews and focus groups.[16]

Adopting a consistent set of clear, plain-language terms as the starting point for improved patient and provider communication and understanding is a critical step in maximizing the potential benefit of novel therapeutic approaches for our patients. We applaud and support the working group's commitment to this goal and encourage our oncology provider colleagues to join us in adopting these recommendations.

AFFILIATIONS

[1]LUNGevity Foundation, Bethesda, MD
[2]Department of Radiation Oncology, UNC/Lineberger Comprehensive Cancer Center, UNC School of Medicine, Chapel Hill, NC
[3]Cancer Risk Assessment and Clinical Cancer Genetics, Departments of Medical Oncology, Cancer Biology, and Urology, Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA
[4]Duke Cancer Institute, Duke University Medical Center, Durham, NC
[5]Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA
[6]Department of Medicine, Division of Oncology, University of Washington, Seattle, WA
[7]Seattle Cancer Care Alliance, Seattle, WA
[8]Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX
[9]Department of Laboratory Medicine and Pathology, University of Washington, Seattle, WA

CORRESPONDING AUTHOR

Nikki A. Martin, MA, PO Box 754, Chicago, IL, 60690; e-mail: nmartin@lungevity.org.

PRIOR PRESENTATION

Presented at the 2020 ASCO Virtual Scientific Program as online abstract e24164, "Using consistent terms in precision medicine to eliminate patient confusion".

SUPPORT

Supported by the LUNGevity Foundation.

AUTHOR CONTRIBUTIONS

Conception and design: Nikki A. Martin, Veda N. Giri, Thomas E. Stinchcombe, Eric Q. Konnick
Administrative support: Nikki A. Martin
Collection and assembly of data: Nikki A. Martin
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/po/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Nikki A. Martin
Stock and Other Ownership Interests: Novartis, Guardant Health, Blueprint Medicines, Isis Pharmaceuticals
Travel, Accommodations, Expenses: Pfizer

Joel E. Tepper
Consulting or Advisory Role: EMD Serono
Other Relationship: Elsevier

Veda N. Giri
Stock and Other Ownership Interests: Novopyxis
Honoraria: Invitae, Ambry Genetics
Speakers' Bureau: Janssen

Thomas E. Stinchcombe
Consulting or Advisory Role: Takeda, AstraZeneca, Genentech/Roche, Foundation Medicine, Pfizer, EMD Serono, Novartis, Daiichi Sankyo, Lilly, Medtronic, Puma Biotechnology, Janssen Oncology, Regeneron, Turning Point Therapeutics, Sanofi/Aventis
Research Funding: Genentech/Roche, Blueprint Medicines, AstraZeneca, Takeda, Advaxis, Regeneron

Heather H. Cheng
Consulting or Advisory Role: AstraZeneca
Research Funding: Sanofi, Janssen, Clovis Oncology, Color Genomics Foundation, Fred Hutchinson Cancer Research Center

Milind M. Javle
Consulting or Advisory Role: QED Therapeutics, OncoSil, Incyte, Mundipharma EDO GmbH, AstraZeneca, Merck, EMD Serono
Other Relationship: Rafael Pharmaceuticals, Incyte, Pieris Pharmaceuticals, Merck, Merck Serono, Novartis, Seattle Genetics, BeiGene, QED Therapeutics, Bayer

Eric Q. Konnick
Honoraria: Ventana Medical Systems, Roche, Clinical Care Options, Medscape, National Comprehensive Cancer Network
Consulting or Advisory Role: River West Meeting Associates
Travel, Accommodations, Expenses: Ventana Medical Systems, Roche, Clinical Care Options LLC, Medscape, National Comprehensive Cancer Network, River West Meeting Associates

No other potential conflicts of interest were reported.

ACKNOWLEDGMENT

The authors thank the following individuals who provided significant contributions to the findings, analysis of our findings, and overall approach: Claire Saxton, MBA, Christie Jett, MS, LCGC, Janine Guglielmino, MA, Becky Bunn, Andrea Miyahira, PhD, Becky Campbell, Rebecca Levine, Stacie Lindsey, Reese Garcia, Marcia Horn, JD, Christine Verini, Victor Gonzalez, Cassadie Moravek, Ronit Yarden, PhD, MHSA, and Sue Friedman, DVM. The Consistent Testing Terminology Working Group (CTTWG) is a partnership of patient groups, providers, professional societies, and industry seeking to promote the adoption of common, plain-language terms about testing for patient communication and education. Editorial and writing services were provided by Wendy Selig, M.S.J., WSCollaborative. The CTTWG is organized under the umbrella of LUNGevity Foundation.

REFERENCES

1. Presley CJ, Tang D, Soulos PR, et al: Association of broad-based genomic sequencing with survival among patients with advanced non-small cell lung cancer in the community oncology setting. JAMA 320:469-477, 2018
2. Gierman HJ, Goldfarb S, Labrador M, et al: Genomic testing and treatment landscape in patients with advanced non-small cell lung cancer (aNSCLC) using real-world data from community oncology practices. J Clin Oncol 37, 2019 (suppl; abstr 1585)
3. Florindez J, Trent J: Low frequency of mutation testing in the United States: An analysis of 3866 GIST patients. Am J Clin Oncol 43:270-278, 2020
4. Gutierrez ME, Price KS, Lanman RB, et al: Genomic profiling for KRAS, NRAS, BRAF, microsatellite instability, and mismatch repair deficiency among patients with metastatic colon cancer. JCO Precis Oncol 3:1-9, 2019
5. Kurian AW, Ward KC, Howlader N, et al: Genetic testing and results in a population-based cohort of breast cancer patients and ovarian cancer patients. J Clin Oncol 37, 2019 (suppl; abstr 1315)
6. Smeltzer MP, Wynes MW, Lantuejoul S, et al: The International Association for the Study of Lung Cancer global survey on molecular testing in lung cancer. J Thorac Oncol 15:1434-1448, 2020
7. Borno HT, Odisho AY, Gunn CM, et al: Disparities in precision medicine—Examining germline genetic counseling and testing patterns among men with prostate cancer. Urol Oncol 39:233.e9-233.e14, 2021
8. Lamba N, Iorgulescu B: Disparities in microsatellite instability/mismatch repair biomarker testing for patients with advanced colorectal cancer. Cancer Epidemiol Biomarkers Prev 29, 2020 (abstr PO-091)
9. Maguire FB, Morris CR, Parikh-Patel A, et al: Disparities in systemic treatment use in advanced-stage non-small cell lung cancer by source of health insurance. Cancer Epidemiol Biomarkers Prev 28:1059-1066, 2019
10. Winston-McPherson GN, Mathias PC, Lockwood CM, et al: Evaluation of patient demographics in clinical cancer genomic testing. J Appl Lab Med 6:119-124, 2021
11. Bruno DS, Hess LM, Li X, et al: Racial disparities in biomarker testing and clinical trial enrollment in non-small cell lung cancer (NSCLC). J Clin Oncol 39, 2021 (suppl; abstr 9005)
12. Mantel S, Roy UB, Ferris A: P2.08-009 need for consistent language around biomarker testing in the diagnosis and treatment of lung cancer: Topic: Other. J Thorac Oncol 12:S1114-S1115, 2017
13. Friedman S, Guglielmino J: Breast Cancer Patients Need More Information on Precision Medicine, Tumor Testing and Genetics, Breast Cancer Patients Need More Information on Precision Medicine, Tumor Testing and Genetics, in (FORCE) LBBCFORCE (ed), 2019, https://www.facingourrisk.org/blog/breast-cancer-patients-need-more-information-on-precision-medicine-tumor-testing-and-genetics
14. Martin NA, Friedman SJ, Saxton C, et al: Using consistent terms in precision medicine to eliminate patient confusion. J Clin Oncol 38, 2020 (suppl; abstr e24164)
15. Konnick EQ, Jett C, Martin NA, et al: A White Paper on the Need for Consistent Testing Terms in Precision Medicine, 2020. https://www.commoncancertestingterms.org/files/Consistent-Testing-Terminology-Whitepaper-070720.pdf
16. Wild D, Grove A, Martin M, et al: Principles of good practice for the translation and cultural adaptation process for patient-reported outcomes (PRO) measures: Report of the ISPOR Task Force for Translation and Cultural Adaptation. Value Health 8:94-104, 2005

Germline Testing in Prostate Cancer: When and Who to Test

Alexandra O. Sokolova, MD[1,2] and Heather H. Cheng, MD, PhD[3,4]

ABSTRACT: The results of multiple studies have shown that a substantial proportion of men with advanced prostate cancer carry germline DNA repair mutations. Germline testing in prostate cancer may inform treatment decisions and consideration for clinical trials. There are 2 FDA approved PARP inhibitors (PARPi), olaparib (Lynparza) and rucaparib (Rubraca), for the treatment of advanced prostate cancer with DNA repair deficiency. Increasing demand for germline testing in prostate cancer and a shortage of genetic counselors have created a need for alternative care models and encouraged oncologists to take a more active role in performing germline testing. This article summarizes recommendations for germline testing in prostate cancer and describes care models for providing counseling and testing.

Introduction

Genetic testing in men with prostate cancer has become more widespread since the discovery that men with metastatic prostate cancer are more likely to carry germline DNA repair gene mutations and the approval of PARP, or poly adenosine diphosphate-ribose polymerase, inhibitors (PARPi) for prostate tumors with DNA repair deficiency. The resulting substantial increase in men with prostate cancer who are eligible for germline testing, with time-sensitive treatment implications, challenges the traditional in-person, time- and resource-intensive cancer genetics care delivery model, and calls for alternative approaches. Urologists, oncologists, and other medical providers are encouraged to take a more active role in delivering germline testing, and they should be aware of current guidelines and optimal pretest and posttest counseling components. This article focuses on the implementation of germline testing in the care of patients with prostate cancer.

PERSPECTIVE

Jun Gong, MD, provides perspective on page 650

Germline vs Other Genetic Testing

Germline genetic testing evaluates for inherited mutations (otherwise known as pathogenic or likely pathogenic variants) that are found in virtually all cells of the body and are derived from the fundamental DNA of an individual. DNA from no cancerous, healthy cells (eg, leucocyte or saliva/buccal swab cells) are used for germline genetic testing. The goals of germline genetic testing are to evaluate for an inherited cancer syndrome; to inform individual and family cancer risks; and to guide cancer prognosis and treatment decisions. Germline testing should be distinguished from recreational and somatic (tumor-specific) testing. Direct-to-consumer recreational genetic testing consists of an at-home test that is advertised to help understand the customer's ancestry. Recreational genetic panels look for inherited variants in saliva/buccal swab cells to inform genealogy, and they are not primarily intended to guide medical decisions as they lack gene coverage and clinical-grade precision. None of the recreational genetic tests include a comprehensive assessment of the *BRCA1/2* or other DNA damage repair genes and are inadequate for medical purposes. Somatic testing panels are designed to identify alterations in a tumor's DNA. A somatic test may occasionally identify mutations expected to be germline, in which case follow-up dedicated germline tests are needed. Examples of somatic panels that

reportgermline mutations include Tempus and UW-Oncoplex. However, many somatic panels use bioinformatics algorithms that may filter out, miss, and/or choose not to report germline mutations. Thus, in general, somatic panels should not be considered adequate for germline conclusions; at most, they should prompt confirmatory germline testing. This article focuses on dedicated clinical-grade germline testing.

Heritable Risks of Prostate Cancer

Germline testing in men with prostate cancer is being performed more often since an important number of prostate cancer cases have a heritable component.[1,2] Germline mutations in DNA repair genes, such as *BRCA1/2*, contribute to hereditary prostate cancer risk and are present in up to 11.8% of men with metastatic prostate cancer,[3] compared with 4.6% among men with localized prostate cancer and 2.7% in persons without a known cancer diagnosis.[3,4]

Germline *BRCA1/2* mutations are associated with increased risk of prostate cancer: up to a 3.8-fold increase with *BRCA1* and an 8.6-fold increase with *BRCA2* mutations.[5] Men who carry germline *BRCA1/2* mutations are not only at increased risk of developing prostate cancer but are also at risk of a more aggressive prostate cancer phenotype.

TABLE 1. Family History Criteria for Germline Testing in Prostate Cancer Patients

Family history of high-risk germline mutations (eg, BRCA1/2, Lynch syndrome)
Ashkenazi Jewish ancestry
Personal history of breast cancer
≥1 first-, second, or third-degree relative with: breast cancer at age <50y; male breast cancer; ovarian cancer; exocrine pancreatic cancer; metastatic, regional, very-high-risk, high-risk prostate cancer at any age
≥1 first-degree relative (father or brother) with prostate cancer at age ≤ 60 (but not clinically localized Grade Group 1)
≥2 first-, second, or third-degree relative with breast cancer or prostate cancer (but not clinically localized Grade Group 1) at any age.
≥3 first- or second-degree relatives with Lynch syndrome-related cancers, especially diagnosed at 50 years or younger: cancers of the biliary tract, endometrium, stomach, ovary, exocrine pancreas, upper tract urothelium, small bowel or colorectal cancer; or glioblastoma

In their study, Castro et al found that patients with prostate cancer with germline *BRCA1/2* mutations at the time of diagnosis were more likely to have higher Gleason score (≥8) and more advanced stage (T3/4, nodal involvement, and metastases) compared with noncarriers. Men with germline *BRCA1/2* mutations also had shorter cancer-specific survival (CSS) than noncarriers (15.7 vs 8.6 years; P=.015).[6] Men with localized prostate cancer and germline *BRCA1/2* mutations have worse outcomes after definitive treatment with surgery or radiation compared with noncarriers: 5-year metastasis-free survival, 72% vs 94%; P <0.001; 5-year CSS, 76% vs 97%; P <0.001.[7] The prospective PROREPAIR-B study found that germline *BRCA2* status is an independent prognostic factor for CSS in patients with metastatic castration-resistant prostate cancer (mCRPC; 17.4 vs 33.2 months; P =.027).[8]

NCCN Guidelines

Based on the study results above and others, the current National Comprehensive Cancer Network (NCCN) guidelines for prostate cancer (version 1.2022)[9] recommend germline testing for the subsets of patients with prostate cancer who are more likely to have germline DNA repair mutations (**Figure 1**).

The NCCN guidelines recommend offering germline testing to the following groups of patients with prostate cancer[9]:

I. Men with node positive, high-risk or very high–risk localized prostate cancer

II. Men with metastatic prostate cancer

III. Men meeting family history criteria (Table 1)

NCCN recommends considering germline testing for men with personal history of prostate cancer and:

I. intermediate risk prostate cancer and intraductal/cribriform histology

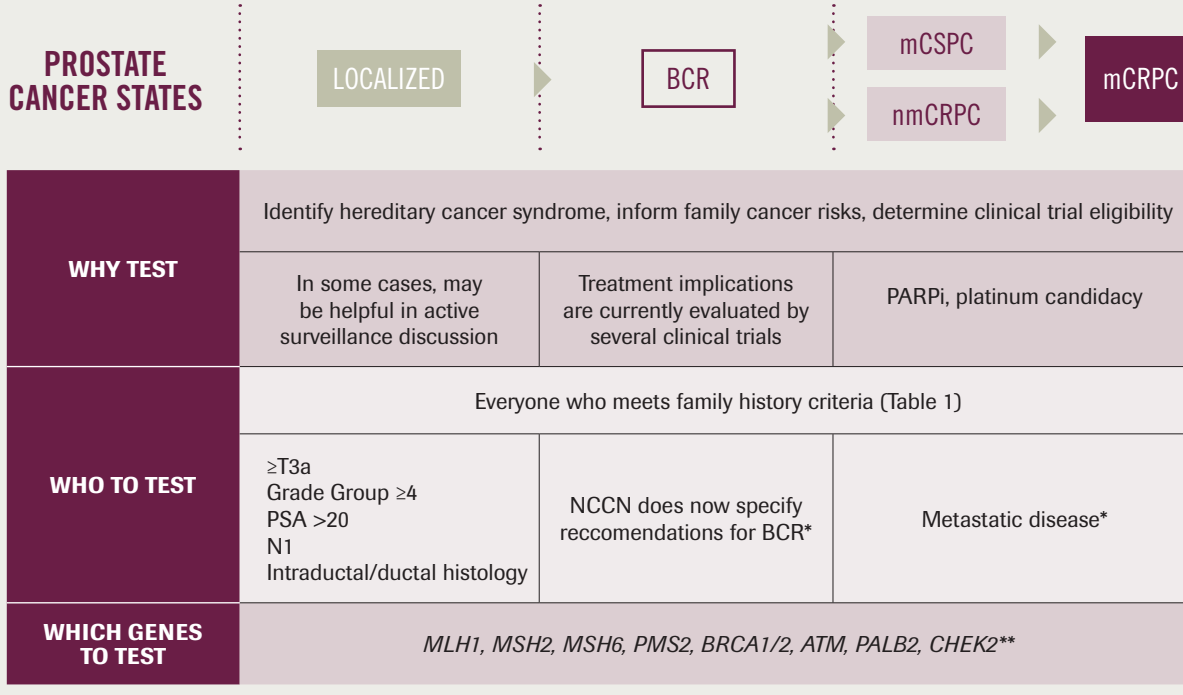
II. personal history of exocrine pancreatic, colorectal, gastric, melanoma, pancreatic, upper tract urothelial, glioblastoma, biliary tract or small intestinal cancers

Several commercial vendors provide germline testing panels, including Invitae, Color, and Ambry. Further details and information on available panels can be found on the vendors' websites. Panel sizes vary from dedicated *BRCA1/2* testing to 91-gene panels. The NCCN guidelines for prostate cancer[9] recommend that germline testing panels include genes associated with Lynch syndrome (*MLH1, MSH2, MSH6, PMS2)* and homologous recombination genes (*BRCA1/2, ATM, PALB2, CHEK2*).[9,10] Broader panels might

TABLE 2. **Care Models to Deliver Germline Testing**

	Traditional	Provider-led	Hybrid
Pretest counseling	Genetic counselor	Provider (eg, oncologist)	Provider (eg, oncologist)
Ordering germline test	Genetic counselor	Provider (eg, oncologist)	Provider (eg, oncologist)
Posttest counseling	Genetic counselor	Provider (eg, oncologist)	Genetic counselor

FIGURE 1. **Recommendations for Germline Testing in Prostate Cancer**
(based on NCCN prostate cancer guidelines, version 1.2022)



*NCCN does not specify recommendations for BCR and nmCRPC | **Other genes may be indicated based on personal and family history

BCR, biochemically recurrent prostate cancer; mCRPC, metastatic castration-resistant prostate cancer; mCSPC, metastatic castration-sensitive prostate cancer; NCCN, National Comprehensive Cancer Network; nmCRPC, nonmetastatic castration-resistant prostate cancer; PARPi, PARP inhibitors; PSA, prostate-specific antigen.

be appropriate for men with mCRPC, especially if clinical trial participation is being considered. Average turnaround time for germline testing is between 10 and 30 days, which varies depending on the particular panel. The cost of germline testing varies depending on insurance coverage. Some companies offer provide testing for a flat out-of-pocket fee (eg, $250), and a benefit of participating in certain research studies may be no-cost testing.

Delivery Care Models for Germline Testing

NCCN guidelines recommend germline testing for a large subset of patients with prostate cancer, but the best care model to offer education and testing is unclear. The traditional clinical care delivery model for cancer genetics includes 2 in-person visits with a genetic counselor, the first for pretest risk assessment and education and the second to discuss the results. This is the most established pathway and, historically, has been utilized the most. However, broadening recommendations for germline testing create great demand that cannot be currently met in a timely fashion by the approximately 4000 genetic counselors in the United States.[11,12] Therefore, oncologists and other providers are increasingly

performing pretest counseling, ordering genetic testing, and providing posttest counseling for their patients, or following hybrid models (**Table 2**).[13]

The provider-led germline testing model has been tested in breast and ovarian cancer but is new in prostate cancer.[14-18] Scheinberg et al reported results of a multicenter prospective study evaluating provider-led germline testing for men with prostate cancer. Twelve oncologists received training about the role of germline testing and in counseling patients, and then offered germline testing to patients with mCRPC in their practice. Those patients who accepted germline testing received pretest counseling and educational materials, and later discussed test results in the oncologist's office. If a germline mutation was identified, the patient was referred to a genetic counselor to discuss the further implications of the results and to initiate cascade testing. Most patients (63 of 66; 95%) accepted the germline testing and high satisfaction rates were achieved among both oncologists and patients.[19] A provider-led germline testing model in the Veterans Affairs health care system was also evaluated. Patients with

TABLE 3. **Response to PARPi in mCRPC Patients Stratified by DNA Repair Gene Mutations**

Study	Agent	Method of response assesment	Number of patients responding to PARPi, by mutation status				
			BRCA1/2	ATM	CDK12	Other HRD mut	No HRD mut
PROFOUND (Hussain et al, 2020)[1]	Olaparib	Imaging	28/84		2/54		N/A
		PSA_{50}	66/153		7/90		N/A
		CTC	29/97		12/56		N/A
TOPARP-A (Mateo et al, 2015)[2]	Olaparib	Imaging, PSA_{50}, CTC	8/8	4/5	N/A	2/3	2/33
TOPARP-B (Mateo et al, 2020)[3]	Olaparib	Imaging, PSA_{50}, CTC	25/30	7/19	5/20	8/27	N/A
TRITON2 (Abida et al, 2020)[4,5]	Rucaparib	Imaging	33/65	2/19	0/10	5/26	N/A
		PSA_{50}	63/115	2/49	1/15	7/26	N/A
NCI study (Karzai et al, 2018)[6]	Durvalumab + olaparib	Imaging, PSA_{50}	7/11	N/A	N/A	N/A	2/6
GALAHAD (Smith et al, 2019)[7]	Niraparib	imaging PSA_{50}, CTC	18/29	N/A	N/A	5/21	N/A
KEYNOTE-365 (Yu et al, 2020)[8]	Olaparib + pembrolizumab	Imaging	5/24				
		PSA_{50}	9/82				
Retrospective analysis (Marshall et al, 2019)[9]	Off-label olaparib	PSA_{50}	13/17	0/6	N/A	N/A	N/A

CTC; circulating tumor cell DNA; imaging, radiographic response measured by RECIST criteria; mCRPC, metastatic castration-resistant prostate cancer; mut, mutations; N/A, not available; PARPi, PARP inhibitors; PSA50, decline of prostate-specific antigen by 50% from baseline; rPFS, radiographic progression-free survival.

metastatic prostate cancer were offered germline testing by their oncologists during regular clinic visits. Pretest counseling was provided by oncologists and study coordinators and saliva for the test was collected in the clinic. Posttest counseling sessions with genetic counselors were provided over the phone by the testing panel company. Again, most patients (190 of 227 approached veterans; 84%) accepted testing, and the test completion rate was 80% (182/227).[20] Results of early studies suggest that provider-led germline testing in prostate cancer could be effective and satisfactory for both patients and providers.

The need to streamline germline testing also calls for the utilization of new technologies, such as video- or phone-based counseling. The EMPOWER study (NCT04598698) assessed men's preference of in-person genetic counseling vs video-based genetic education[21]; results indicated that in-person genetic counseling was preferred by men with less education and higher anxiety levels, and it resulted in greater improvement of cancer genetics knowledge. The rates of genetic testing uptake were similar for video-based and in-person counseling groups.[21] Video-based counseling was also evaluated by Tong et al, who compared 2 models of streamlined germline testing in prostate cancer: (a) a take-home genetic kit provided by an oncologist, followed by referral to a genetic counselor if subsequent results are concerning; and (b) a genetic testing station, at which the patient participated in a video call from a genetic counseling assistant for genetics education and collection of family history, which was followed by saliva sample collection and, later, referral to a genetic counselor if any mutation was identified. The latter approach resulted in a lower rate of incomplete tests and a higher rate of follow-up with genetic counselors for positive results. Authors suggested that utilization of video education and involvement of genetic counselor assistants may improve access to germline testing among patients with prostate cancer.[22] Several studies are ongoing to evaluate other care models to provide genetic testing in prostate cancer (eg, NCT02917798, NCT03076242, NCT03328091, NCT03503097).[23]

Components of Germline Testing Counseling

Oncologists who choose to perform germline testing need to be comfortable with several aspects of genetic counseling and to remain current on the ethics of informed consent and posttest counseling for germline testing (**Figure 2**). The 2019 Philadelphia Prostate Cancer Consensus Conference suggests that optimal pretest consent should include discussion of the purpose of testing, types of possible results (ie, pathogenic/likely pathogenic; benign/likely benign; variant of unknown significance; no variants identified), the possibility of identifying hereditary cancer syndrome and/or other cancer risks, testing's potential cost, the importance of cascade family testing, and the Genetic Information Nondiscrimination Act (GINA) law.[12] The GINA law protects against discrimination based on genetics in employment and health insurance; however, it is not applicable to life insurance, long-term care disability insurance, Indian Health services, and patients enrolled into federal employee, Veterans Administration, and US military health benefit plans.[23,24] These gaps in protection by GINA law are important to discuss with patients, who may need to consider them before proceeding with the germline testing. Providers should also consider discussing the different panels available for testing, the privacy of genetic tests, and

FIGURE 2. **Germline Testing Steps**

PRETEST COUNSELLING

Should include discussion of:

- the goal for testing
- possible results
- potential to identify hereditary cancer syndrome and additional cancer risks
- cost of testing
- cascade family testing
- Genetic Information Nondiscrimination Act (GINA) law

ORDER TEST

When choosing a panel, consider:

- patient preferences
- genes included in the panel
- Out-of-pocket cost to patient
- data sharing/selling policies of genetic laboratories
- genetic counselor support provided by genetic laboratories

POSTTEST COUNSELLING

Should include discussion of:

- treatment implications
- implications of other cancer risks
- cascade genetic testing
- VUS reclassification potential
- family cancer risk based on family and personal history, if no mutation identified

genetic laboratories' policies related to sharing and selling of data.[12]

Providers ordering germline tests also must accept responsibility to follow up with patients if reclassification occurs of a variant of (currently) unknown significance (VUS). VUS are reported in about 30% of men with prostate cancer who undergo germline testing.[4] VUS results do not change clinical recommendations, and the majority of them end up being reclassified as benign.[25,26] In the Find My Variant Study, 38 of 63 VUS (61%) were reclassified: 32 of 38 (84%) as benign/likely benign and 6 of 38 (16%) as pathogenic/likely pathogenic.[27,28] In the rare case when a VUS is reclassified as pathogenic or likely pathogenic, the provider who ordered the test is notified and they are responsible for disclosing the reclassification to the patient. Regardless of the model used, genetic counselor referral is recommended if a patient has a germline mutation identified and/or if clinical suspicion is high for an inherited cancer predisposition. Collaborative efforts are needed to educate oncology providers on aspects of germline testing counseling and to create shared printed and video resources for patients to facilitate informed consent.

Cascade Testing

Germline testing in men with prostate cancer can potentially benefit not only the patient but also family members. If a germline mutation is identified in a patient, testing for the same mutation in family members (cascade testing) should be performed. For instance, identifying family members with *BRCA1/2* mutations could inform potentially lifesaving risk-reducing interventions, eg, prophylactic salpingo-oophorectomy for female *BRCA1* mutation carriers. The IMPACT study (Identification of Men with a Genetic Predisposition to Prostate Cancer: Targeted screening in g*BRCA1/2* mutation carriers and controls) evaluated the utility of prostate-specific antigen (PSA) screening in men aged 40 to 69 years with germline *BRCA1/2* mutations compared with its utility in noncarriers.[29,30] The study enrolled 3027 men with no personal history of prostate cancer: 919 *BRCA1* carriers, 902 *BRCA2* carriers, 709 *BRCA1* noncarriers, and 497 *BRCA2* noncarriers. Preliminary results, reported after 3 years of follow-up, showed that *BRCA2* mutation carriers, compared with noncarriers, have a higher incidence of prostate cancer and a younger age of diagnosis. The results for *BRCA1* carriers were not definitive, and further investigation is needed. The results from IMPACT suggest annual PSA screening for *BRCA2* mutation carriers aged between 40 and 69 years, using PSA cutoff of 3.0 ng/ml.[30] Studies evaluating the predictive value of lower PSA cutoff and prostate MRI are ongoing (eg, NCT03805919, NCT01990521).

PERSPECTIVE BY

Jun Gong, MD

An Evolving Relationship Between Medical Oncologists and Genetic Counselors in Prostate Cancer

The authors of this timely review are to be applauded for providing a comprehensive analysis of the current literature supporting guidelines-based indications for germline testing in prostate cancer. As they describe, germline mutations in DNA repair genes, including *BRCA*1/2, can be found in a clinically significant proportion of men with metastatic prostate cancer—up to 11.8%.[1] The impact of these germline mutations on the modern care of the patient with prostate cancer is multifold.

As the authors highlight, the presence of germline mutations in DNA repair genes can guide use of FDA-approved targeted agents in refractory and advanced prostate cancer, specifically the PARP inhibitors (PARPi) olaparib (Lynparza) and rucaparib (Rubraca). In the setting of DNA repair deficiency, sensitivity to platinum chemotherapy has also been well described. These associations have direct relevance to us, as medical oncologists, in our clinical management of patients with metastatic prostate cancer. It should be noted that 2 additional PARPi, talazoparib (Talzenna) and niraparib (Zejula), are separately undergoing phase 3 trials randomizing patients with metastatic castrate-resistant prostate cancer (mCRPC) who have not received systemic therapy in the castrate-esistant setting. Both of these trials seek to explore the effectiveness of moving PARPi to earlier settings in mCRPC with novel hormonal therapy in those with and without DNA damage repair deficiencies.[2] As mentioned in the article, PARPi are also moving into the localized, high-risk prostate cancer setting; my group is participating in the NRG-GU007 (NADIR; NCT04037254) phase 2 trial in this setting, investigating niraparib in combination

with standard-of-care radiation therapy and androgen deprivation therapy in patients with high-risk prostate cancer. As such, reasons for somatic and germline testing in prostate cancer are likely to evolve and expand in the near future.

Beyond the influence of germline testing on treatment decisions for our patients with metastatic prostate cancer, we cannot emphasize enough the importance of germline testing for patients' families in patients who are positive for germline testing with our colleagues in genetic counseling. Here, the authors importantly highlight different care models to deliver germline testing. This topic has become increasingly relevant, given concerns for broadened recommendations for genetic testing and the resultant great demand that cannot be currently met by approximately 4000 genetic counselors in the United States.

One solution to this increased demand is the provider-led testing model, in which the oncologist performs the pretest counseling and discusses posttest results, with eventual referral to genetic counseling if there is a positive genetic test result. Similar models are also being described with primary care providers and genetic counselors.[3] Such provider-led models are in accordance with the American Society of Clinical Oncology's genetic testing guidelines, in that experienced clinicians who are not geneticists may provide pretest counseling so long as prior informed written consent from the patient is obtained. Important to the success of this model would likely be the degree of clinician experience (ie, how comprehensive their genetic counseling training has been), the clinician's comfort level, and the supporting staff or resources available to the clinician to operate a provider-led germline testing model.[4]

Members of a consensus panel discussing germline testing have pointed out that clinicians who lack genetics training may experience numerous obstacles when counseling patients, in particular obstacles related to limited knowledge of the downstream impact of genetic testing, such as health insurance coverage, implications for life insurance, and protections afforded by the Genetic Information Nondiscrimination Act.[5] Discussions about the importance and management of variants of unknown significance could be confusing for the patient even in the posttesting stage without appropriate knowledge and training on the clinician's part. In addition, genetic counseling may not always be reimbursed by some insurers, such as Medicare and Medicaid.

The hybrid model as presented by the authors may allow oncologists to shoulder some of the burdens of pretest counseling and ordering germline testing, while the experienced genetic counselors take over in the posttest counseling stage. To additionally lessen the burdens on genetic counselors, limiting the number of in-person visits by patients may be another option. As we have all learned throughout the COVID-19 pandemic, telemedicine does have certain advantages in clinical practice. Mauer et al have described the value of virtual counseling and technological adaptations, including billing practices and coordination of education and outreach opportunities, that have been made during the pandemic and have helped genetic counselors.[6] Such adaptations represent only a few of the evolving strategies that we as medical oncologists, in conjunction with our health care team, must seek out and implement to help our genetic counseling colleagues reach an expanding population of prostate cancer patients in need of evidence-based germline testing.

REFERENCES

1. Pritchard CC, Mateo J, Walsh MF, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. *N Engl J Med.* 2016;375(5):443-453. doi:10.1056/NEJMoa1603144

2. Gong J, Posadas E, Bhowmick N, et al. Integrating PARP inhibitors into advanced prostate cancer therapeutics. *Oncology (Williston Park).* 2021;35(3):119-125. doi: 10.46883/ONC.2021.3503.0119

3. Carroll JC, Morrison S, Miller FA, Wilson BJ, Permaul JA, Allanson J. Anticipating the primary care role in genomic medicine: expectations of genetics health professionals. *J Community Genet.* Published online August 11, 2021. doi: 10.1007/s12687-021-00544-1

4. Robson ME, Bradbury AR, Arun B, et al. American Society of Clinical Oncology policy statement update: genetic and genomic testing for cancer susceptibility. *J Clin Oncol.* 2015;33(31):3660-3667. doi:10.1200/JCO.2015.63.0996

5. Bratslavsky G, Mendhiratta N, Daneshvar M, et al. Genetic risk assessment for hereditary renal cell carcinoma: clinical consensus statement. *Cancer.* Published August 3, 2021. doi:10.1002/cncr.33679

6. Mauer C, Zimmerman J, Lahiri S, et al. Adapting genetic counseling operations amidst the COVID-19 pandemic. *J Genet Couns.* 2021;30(4):949-955. doi:10.1002/jgc4.1474

Gong is a is a medical oncologist of the Gastrointestinal Disease Research Group, Pancreatic Cancer Research Group, and Urologic Oncology Program in the Samuel Oschin Comprehensive Cancer Institute at Cedars-Sinai.

Oncologists are encouraged to take a more active role in performing germlinetesting, but the optimal approach is unclear...joint efforts are needed to build collaborative relationships between oncologists and genetic specialists.

Treatment Implications of Germline Testing

Advanced disease

PARPi. Patients with DNA repair mutations have higher response rates to PARPi and platinum chemotherapy.[31,32] In 2020, two PARPi received FDA approval for treatment of mCRPC with germline or somatic DNA damage repair gene mutations. Rucaparib was approved based on the phase 2 TRITON2 (NCT02952534) study; it reported a 51% (50/98) radiographic response rate among men with mCRPC and *BRCA1/2* alterations.[33] The benefit for men with non-*BRCA* DNA repair mutations was less clear, and rucaparib is currently approved only for carriers of *BRCA1/2* mutations.[33-35] The olaparib label includes a larger number of mutated genes eligible for treatment (*BRCA1, BRCA2, ATM, BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L)*, based on results of the phase 3 ProFOUND study (NCT02987543). ProFOUND compared olaparib with enzalutamide or abiraterone and showed improved radiographic progression-free survival (5.8 months vs 3.5 months) with olaparib.[36] Several other ongoing studies are evaluating the efficiency of PARPi monotherapy and combined therapies in mCRPC. **Table 3** summarizes study results reporting response rates to PARPi in prostate cancer.[37]

Platinum chemotherapy. Historically, platinum chemotherapy has been used to treat tumors, such as ovarian or pancreatic cancer, that have a high frequency of DNA repair mutations.[38,39] Early data suggest that platinum chemotherapy is also effective in prostate tumors with DNA repair deficiency.[40-43] A retrospective case series by Cheng et al showed that 3 of 3 patients with prostate cancer who had biallelic inactivation of *BRCA2* had an exceptional response to platinum chemotherapy after progressing on several therapies.[40] The results of a larger retrospective study supported this observation, reporting that 75% (6/8) of patients with mCRPC and with germline *BRCA2* mutations had a PSA_{50} response (ie, decline of prostate-specific antigen by 50% from baseline) to platinum chemotherapy compared with 17% (23/133) of mCRPC patients without g*BRCA2* mutations.[41] Mota et al reported a 53% (8/15) PSA_{50} response to platinum chemotherapy among men with mCRPC and DNA damage repair mutations (ie, *BRCA2, BRCA1, ATM, PALB2, FANCA*, and *CDK12*).[43]

Localized Disease

NCCN guidelines recommend considering DNA repair mutation status when discussing the possibility of active surveillance. Germline mutations in *BRCA1/2* or *ATM* are associated with a higher likelihood of grade reclassification among men undergoing active surveillance.[44] Mutation carriers should be closely monitored; they could potentially benefit from an earlier definitive treatment approach.

BRCA1/2 carriers have worse outcomes with conventional definitive therapies. Castro et al evaluated the response of *BRCA1/2* carriers with localized prostate cancer to 2 radical treatments—definitive radiation and radical prostatectomy—and reported that *BRCA* status is an independent prognostic factor for metastasis-free survival (HR, 2.36; $P = .002$) and CSS (HR, 2.17; $P = .016$).[7] New treatment approaches in earlier disease stages are being evaluated in clinical trials for patients with prostate cancer and DNA repair deficiency. Targeted therapies, such as PARPi, are being actively investigated in the biochemically recurrent stage of prostate cancer (eg, NCT03047135, NCT03810105, NCT04336943, NCT0353394) and as neoadjuvant therapy in localized disease (eg, NCT04030559).

Conclusions

Germline testing is becoming more commonplace with advances in precision oncology and expanding treatment implications of the results of this testing. The NCCN prostate cancer guidelines recommend germline testing for men with high-risk or very high–risk localized prostate cancer; men with metastatic prostate cancer; patients with intraductal histology of the prostate; and patients meeting family history criteria. These recommendations have created a need for germline testing of many prostate cancer patients, which calls for a change in the traditional cancer genetics delivery model to meet the new demand.[45] Oncologists are encouraged to take a more active role in performing germline testing, but the

optimal approach is unclear. Until the results of larger trials focusing on various testing delivery models are available, joint efforts are needed to build collaborative relationships between oncologists and genetic specialists. Further efforts are required to create dedicated resources to support providers in this new era of genetic testing and precision oncology in prostate cancer, which is marked by near-constant change.

AFFILIATIONS:
[1]Division of Medical Oncology, Oregon Health Science University (OHSU).
[2]OHSU Knight Cancer Institute.
[3]Division of Medical Oncology, University of Washington.
[4]Division of Clinical Research, Fred Hutch Cancer Research Center.

ACKNOWLEDGMENTS: We gratefully acknowledge support from the Institute for Prostate Cancer Research, NIH/NCI CCSG P30 CA015704, NIH SPORE CA097186, NCI T32CA009515 award, Congressional Designated Medical Research Program (CDMRP) award W81XWH-17-2-0043, and the Prostate Cancer Foundation.

CONFLICT OF INTEREST DISCLOSURE:
AOS has no conflicts to disclose; HHC receives research funding to her institution from Clovis Oncology, Color Genomics, Janssen Pharmaceuticals, Medivation, Inc. (Astellas Pharma Inc), Phosplatin Therapuetics, and Sanofi S.A., and has a consulting or advisory role with AstraZeneca.

KEY REFERENCES

1. Mucci LA, Hjelmborg JB, Harris JR, et al; Nordic Twin Study of Cancer (NorTwinCan) Collaboration. Familial risk and heritability of cancer among twins in Nordic countries. *JAMA*. 2016;315(1):68-76. doi:10.1001/jama.2015.17703

2. Hjelmborg JB, Scheike T, Holst K, et al. The heritability of prostate cancer in the Nordic Twin Study of Cancer. *Cancer Epidemiol Biomark Prev.* 2014;23(11):2303-2310. doi:10.1158/1055-9965.EPI-13-0568

3. Pritchard CC, Mateo J, Walsh MF, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. *N Engl J Med*. 2016;375(5):443-453. doi:10.1056/NEJMoa1603144

4. Nicolosi P, Ledet E, Yang S, et al. Prevalence of germline variants in prostate cancer and implications for current genetic testing guidelines. *JAMA Oncol*. 2019;5(4):523-528. doi:10.1001/jamaoncol.2018.6760

5. Giri VN, Beebe-Dimmer JL. Familial prostate cancer. *Semin Oncol*. 2016;43(5):560-565. doi:10.1053/j.seminoncol.2016.08.001

6. Castro E, Goh C, Olmos D, et al. Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. *J Clin Oncol.* 2013;31(14):1748-1757. doi:10.1200/JCO.2012.43.1882

7. Castro E, Goh C, Leongamornlert D, et al. Effect of BRCA mutations on metastatic relapse and cause-specific survival after radical treatment for localised prostate cancer. *Eur Urol*. 2015;68(2):186-193. doi:10.1016/j.eururo.2014.10.022

8. Castro E, Romero-Laorden N, Del Pozo A, et al. PROREPAIR-B: a prospective cohort study of the impact of germline DNA repair mutations on the outcomes of patients with metastatic castration-resistant prostate cancer. *J Clin Oncol*. 2019;37(6):490-503. doi:10.1200/JCO.18.00358

9. NCCN Clinical Practice Guidelines in Oncology. Prostate cancer, version 1.2022. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed 9/10/2021

10. Cheng HH, Sokolova AO, Schaeffer EM, Small EJ, Higano CS. Germline and somatic mutations in prostate cancer for the clinician. *J Natl Compr Cancer Netw*. 2019;17(5):515-521. doi:10.6004/jnccn.2019.7307

11. Abacan MA, Alsubaie L, Barlow-Stewart K, et al. The global state of the genetic counseling profession. *Eur J Hum Genet*. 2019;27(2):183-197. doi:10.1038/s41431-018-0252-x

12. Giri VN, Knudsen KE, Kelly WK, et al. Implementation of germline testing for prostate cancer: Philadelphia Prostate Cancer Consensus Conference 2019. *J Clin Oncol*. 2020;38(24):2798-2811. doi:10.1200/JCO.20.00046

13. Giri VN, Hyatt C, Gomella LG. Germline testing for men with prostate cancer: navigating an expanding new world of genetic evaluation for precision therapy and precision management. *J Clin Oncol*. 2019;37(17):1455-1459. doi:10.1200/JCO.18.02181

14. George A, Riddell D, Seal S, et al. Implementing rapid, robust, cost-effective, patient-centred, routine genetic testing in ovarian cancer patients. *Sci Rep*. 2016;6:29506. doi:10.1038/srep29506

15. Yoon SY, Bashah NSAhmad, Wong SW, et al. LBA4_PR. Mainstreaming genetic counselling for genetic testing of BRCA1 and BRCA2 in ovarian cancer patients in Malaysia (MaGiC study). *Ann Oncol*. 2017;28(suppl 10):x187. doi:10.1093/annonc/mdx729.004

16. Enomoto T, Aoki D, Hattori K, et al. The first Japanese nationwide multicenter study of BRCA mutation testing in ovarian cancer: CHARacterizing the cross-sectionaL approach to Ovarian cancer geneTic TEsting of BRCA (CHARLOTTE). *Int J Gynecol Cancer*. 2019;29(6):1043-1049. doi:10.1136/ijgc-2019-000384

For references visit cancernetwork.com/SOKOLOVA_10.21

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Prostate Cancer

Editorial by Elena Castro on pp. 251–252 of this issue

Inherited TP53 Variants and Risk of Prostate Cancer

Kara N. Maxwell [a,b,x,†], Heather H. Cheng [c,d,†], Jacquelyn Powers [a,†], Roman Gulati [d], Elisa M. Ledet [e], Casey Morrison [f], Anh Le [a], Ryan Hausler [a,y], Jill Stopfer [g], Sophie Hyman [g], Wendy Kohlmann [h], Anne Naumer [h], Jennie Vagher [h], Samantha E. Greenberg [h], Lorraine Naylor [i], Mercy Laurino [i], Eric Q. Konnick [j], Brian H. Shirts [j,u], Saud H. AlDubayan [k,l], Eliezer M. Van Allen [k,l], Bastien Nguyen [m], Joseph Vijai [n], Wassim Abida [o], Maria I. Carlo [o], Marianne Dubard-Gault [i,w], Daniel J. Lee [p,x], Luke D. Maese [h,q], Diana Mandelker [r], Bruce Montgomery [c,d,z], Michael J. Morris [o], Piper Nicolosi [s], Robert L. Nussbaum [s], Lauren E. Schwartz [f], Zsofia Stadler [o], Judy E. Garber [g], Kenneth Offit [n], Joshua D. Schiffman [h,q,t], Peter S. Nelson [d,i], Oliver Sartor [e], Michael F. Walsh [o,v,‡], Colin C. Pritchard [j,u,‡,]*

[a] *Division of Hematology/Oncology, Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA;* [b] *Department of Genetics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA;* [c] *Division of Oncology, Department of Medicine, University of Washington, Seattle, WA, USA;* [d] *Fred Hutchinson Cancer Research Center, Seattle, WA, USA;* [e] *Tulane Cancer Center, Tulane Medical School, New Orleans, LA, USA;* [f] *Department of Pathology and Laboratory Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA;* [g] *Division of Population Sciences, Dana-Farber Cancer Institute, Boston, MA, USA;* [h] *Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA;* [i] *Seattle Cancer Care Alliance, Seattle, WA, USA;* [j] *Department of Laboratory Medicine and Pathology, University of Washington, Seattle, WA, USA;* [k] *Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA;* [l] *Cancer Program, The Broad Institute of MIT and Harvard, Cambridge, MA, USA;* [m] *Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, USA;* [n] *Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA;* [o] *Division of Solid Tumor Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA;* [p] *Department of Surgery, Division of Urology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA;* [q] *Department of Pediatrics, University of Utah School of Medicine, Salt Lake City, UT, USA;* [r] *Diagnostic Molecular Genetics Laboratory, Memorial Sloan Kettering Cancer Center, New York, NY, USA;* [s] *Invitae Corporation, San Francisco, CA, USA;* [t] *PEEL Therapeutics, Inc., Salt Lake City, UT, USA;* [u] *Brotman Baty Institute for Precision Medicine, Seattle, WA, USA;* [v] *Department of Pediatrics, Memorial Sloan Kettering Cancer Center, New York, NY, USA;* [w] *Division of Medical Genetics, Department of Medicine, University of Washington, Seattle, WA, USA;* [x] *Corporal Michael J. Crescenz Veterans Affairs Medical Center, Philadelphia PA, 19104;* [y] *George E. Wahlen Department of Veterans Affairs Medical Center, Salt Lake City, UT 84148;* [z] *VA Puget Sound Health Care System, Seattle, WA 98108*

Article info

Article history:
Accepted October 28, 2021

Associate Editor:
James Catto

Abstract

Background: Inherited germline *TP53* pathogenic and likely pathogenic variants (g*TP53*) cause autosomal dominant multicancer predisposition including Li-Fraumeni syndrome (LFS). However, there is no known association of prostate cancer with *gTP53*.
Objective: To determine whether *gTP53* predisposes to prostate cancer.
Design, setting, and participants: This multi-institutional retrospective study characterizes prostate cancer incidence in a cohort of LFS males and g*TP53* prevalence in a prostate cancer cohort.

† These first authors contributed equally to this manuscript.
‡ These last authors contributed equally to this manuscript.
* Corresponding author. Department of Laboratory Medicine and Pathology, University of Washington, 1959 NE Pacific Street, Seattle, WA 98195, USA. Tel. +1 (206) 598-6131; Fax: 1 (206) 543-3644.
E-mail address: cpritch@uw.edu (C.C. Pritchard).

https://doi.org/10.1016/j.eururo.2021.10.036

Keywords:
Attenuated
Genetic testing
Germline
Hypomorphic mutation
Inherited cancer syndrome
Li-Fraumeni syndrome
Pathogenic variant
Prostate cancer
Screening
TP53

Outcome measurements and statistical analysis: We evaluated the spectrum of g*TP53* variants and clinical features associated with prostate cancer.
Results and limitations: We identified 31 prostate cancer cases among 163 adult LFS males, including 26 of 54 aged ≥50 yr. Among 117 LFS males without prostate cancer at the time of genetic testing, six were diagnosed with prostate cancer over a median (interquartile range [IQR]) of 3.0 (1.3–7.2) yr of follow-up, a 25-fold increased risk (95% confidence interval [CI] 9.2–55; $p < 0.0001$). We identified g*TP53* in 38 of 6850 males (0.6%) in the prostate cancer cohort, a relative risk 9.1-fold higher than that of population controls (95% CI 6.2–14; $p < 0.0001$; gnomAD). We observed hotspots at the sites of attenuated variants not associated with classic LFS. Two-thirds of available g*TP53* prostate tumors had somatic inactivation of the second *TP53* allele. Among g*TP53* prostate cancer cases in this study, the median age at diagnosis was 56 (IQR: 51–62) yr, 44% had Gleason ≥8 tumors, and 29% had advanced disease at diagnosis.
Conclusions: Complementary analyses of prostate cancer incidence in LFS males and g*TP53* prevalence in prostate cancer cohorts suggest that g*TP53* predisposes to aggressive prostate cancer. Prostate cancer should be considered as part of LFS screening protocols and *TP53* considered in germline prostate cancer susceptibility testing.
Patient summary: Inherited pathogenic variants in the *TP53* gene are likely to predispose men to aggressive prostate cancer.

1. Introduction

Prostate cancer (PrCa) is a highly heritable disease [1]. Recent data have demonstrated that approximately 5–20% of cases are associated with germline (inherited) pathogenic variants in genes associated with recognized cancer predisposition syndromes, such *BRCA2* and *ATM* [2,3]. Germline *TP53* pathogenic variants (g*TP53*) are associated with an autosomal dominant hereditary multicancer predisposition known as Li-Fraumeni syndrome (LFS) [4,5]. Patients with classic LFS develop early-onset, pediatric, and multiple primary cancers with nearly universal development of at least one cancer in their lifetime [6]; presentations with more variable penetrance are increasingly observed [5,7,8]. Panel genetic testing, largely ascertained on individuals with personal and family histories of breast cancers, has demonstrated a more expansive tumor spectrum and more variable penetrance of g*TP53* variants than previously appreciated [9]. However, there has been no documented association of PrCa with g*TP53*, outside of one case report [10]. In a recent review of the *TP53* International Agency for Research on Cancer (IARC) database [8], only 1.7% of g*TP53* patients were reported to have PrCa, far lower than the 14% lifetime risk of PrCa for average men in the USA [11]. However, this analysis is misleading given that the database is heavily skewed toward men of younger ages than those relevant to typical PrCa risk.

Guidelines advise extensive cancer screening in patients with LFS, starting in childhood, for example, yearly full-body magnetic resonance imaging (MRI) and brain imaging, targeted ultrasound, assessments for gastrointestinal and skin neoplasms, and breast screening for women [12,13]. Patients with LFS may also have an elevated risk of post-treatment secondary malignancies, for example, after radiation [14,15]. Therefore, LFS status may be considered in cancer treatment planning. For example, in women with LFS, total mastectomy is preferred to partial mastectomy to avoid the need for radiation.

Current cancer screening guidelines for LFS patients do not include PrCa. Moreover, g*TP53* status is not currently considered in treatment planning for individuals with PrCa, which often includes decisions between radiation and surgery for patients with early-stage localized disease and regarding adjuvant or salvage radiation in those with later-stage or recurrent disease. Herein, we analyze LFS cohort data alongside laboratory-based clinical genetic testing data in PrCa cohorts, and we demonstrate that g*TP53* is associated with the development of aggressive PrCa.

2. Patients and methods

2.1. LFS and PrCa cohorts

The LFS cohort (n = 163 males from 132 families) was created from four datasets of families with a diagnosis of LFS (Supplementary Table 1 and Supplementary material) from Dana Farber Cancer Institute, Huntsman Cancer Institute, Memorial Sloan Kettering Cancer Center, and the University of Pennsylvania. Eligibility criteria for index cases from LFS families were as follows: (1) male sex, (2) age at last follow-up ≥18 yr, and (3) genetic testing confirming heterozygous g*TP53* or obligate carrier status within a family. Dates of genetic testing, PrCa diagnosis, or last follow-up and/or death were collected for all LFS men (Supplementary Table 1). The PrCa cohort (n = 6850 individuals) was created from four large series of PrCa patients who had undergone tumor or tumor/germline sequencing (Supplementary material). Pedigrees of patients in both cohorts were collected and examined to ensure that PrCa cases were not double counted due to enrollment in LFS registries or sequencing at more than one institution (Supplementary Fig. 1). Clinical data for both cohorts were collected in accordance with the Declaration of Helsinki guidelines and following approval from the respective institutional review boards at University of Washington, Tulane University, University of Pennsylvania, University of Utah, Memorial Sloan Kettering Cancer Institute, and Dana Farber Cancer Institute.

2.2. TP53 variant review and exclusion of somatic interference

All variants in the LFS and PrCa cohorts were referenced with ClinVar [16] and classified based on *TP53*-specific American College of Medical Genetics (ACMG) guidelines (Supplementary material) [17]. Subclassification of likely pathogenic or pathogenic variants as full penetrance versus attenuated variants was based on published functional data. Patients in the LFS cohorts were confirmed to have germline variants not due to somatic interference by clonal hematopoiesis of indeterminate potential or other abnormal clonal expansion [18] by testing of ancillary tissues and/or by variant segregation in families. In the PrCa cohorts, somatic interference [18] was excluded by: first, restricting to pathogenic and likely pathogenic variants with >35% variant fraction in blood; second, tumor sequencing when available to confirm presence in the cancer and in the matched normal tissue; and finally, a comparison of variant allele fractions with other observed somatic and germline variants.

2.3. Tumor analyses

Tumor next-generation sequencing data (UW-OncoPlex and MSK-IMPACT) were available for a subset of g*TP53* carriers [19,20]. Tumor data were analyzed by an expert molecular pathologist (C.C.P.) for evidence of somatic *TP53* second allele inactivation, including assessment of loss of heterozygosity (L.O.H.).

2.4. Statistical analysis

To calculate PrCa risk and incidence rates, the full LFS cohort was restricted to patients without a prior PrCa diagnosis at genetic testing to avoid selection and immortality biases. Risk of PrCa diagnosis relative to the general population was then estimated using a standardized incidence ratio (SIR) comparing the observed numbers with the expected numbers of PrCa diagnoses, with the latter calculated by applying PrCa incidence rates in the population to specific ages and calendar years of follow-up. Follow-up was summarized using reverse Kaplan-Meier estimation [21], which begins at the genetic test, treats death or last follow-up without PrCa diagnosis as events, and censors PrCa diagnoses. This approach gives a robust summary of follow-up for all patients, which is used to calculate the expected number of PrCa diagnoses. The PrCa incidence rates were those observed in the Surveillance, Epidemiology, and End Results (SEER) program from 1997 to 2017 by calendar year and 5-yr age group. Incidence rates over the period of 2018–2020 were assumed to be equal to the rates observed in 2017. Significance of the SIR was evaluated using a two-sided exact Poisson test. Overall and age-specific PrCa incidence rates in the restricted cohort were calculated relative to observed person-years of follow-up, and corresponding rates in SEER were calculated relative to population totals. In the PrCa cohort, the relative risk of carrying g*TP53* was compared with frequencies in the gnomAD database using a Fisher's exact test after excluding individuals with cancer (gnomAD v2.1.1 noncancer, 134 187 samples; Supplementary material).

3. Results

3.1. Incidence of PrCa in LFS

Among a cohort of LFS individuals created from datasets at four academic institutions, we identified 163 males aged ≥18 yr with a confirmed g*TP53* likely pathogenic/pathogenic variant or obligate carrier status from 132 families (Supplementary Tables 1 and 2, and Supplementary Fig. 1). We identified PrCa in 31 of 163 (19%) adult males in this cohort, including 26 of 54 males (48%) aged ≥50 yr (Table 1). The frequency of PrCa within age deciles was similar in all four datasets (Supplementary Table 3). In a restricted analysis of 117 men who did not have a PrCa diagnosis at the time of genetic testing (Supplementary Table 1), six were diagnosed with PrCa over a median (interquartile range [IQR]) of 3.0 (1.3–7.2)s of follow-up. The risk of a PrCa diagnosis in this subgroup of LFS men was 25 times that in the general population (95% confidence interval [CI] 9.2–55; $p < 0.0001$), with incidence rates significantly elevated at all ages (Fig. 1, Table 2, and Supplementary Fig. 2).

Table 1 – Age distribution of men with prostate cancer (PrCa) in Li-Fraumeni syndrome (LFS) cohorts

Age group	Combined LFS/LFL cohorts		
	n	PrCa	%
18–29	32	0	0
30–39	35	1	2.9
40–49	42	4	10
50–59	32	15	47
60–69	15	7	47
70–79	7	4	57
≥80	0	0	NA
Total (w/ages)	163	31	19

LFL = Li-Fraumeni–like syndrome; NA = not available.
(1) Age based on cancer diagnosis age or current age if unaffected.

3.2. Prevalence of gTP53 in individuals with prostate cancer

To determine the prevalence of g*TP53* in PrCa patients, we analyzed four large germline or tumor sequencing datasets comprising 6850 PrCa patients (Table 3 and Supplementary Table 2), excluding cases suggestive of somatic interference [18]. We identified g*TP53* in 38 patients overall (0.55% prevalence), with prevalence rates ranging from 0.27% to 0.84% across the four independent cohorts (Table 3). The relative risk of having g*TP53* was significantly elevated at 9.1 (95% CI 6.2–14, $p < 0.0001$) compared with the gnomAD noncancer population database (Fig. 1). Restricting both the sequencing cohorts and the gnomAD to *TP53* variants classified as likely pathogenic or pathogenic in ClinVar, the relative risk remained statistically significantly elevated at 8.7 (95% CI 4.8–16, $p < 0.0001$; Table 3).

3.3. Spectrum of gTP53 variants reveals hotspots associated with attenuated mutations

To study the spectrum of *gTP53* variants and clinicopathological PrCa features, we combined g*TP53* PrCa cases from the LFS and PrCa cohorts as no significant differences were observed for any variable between cohorts (Table 4). Of 67 individuals with PrCa and g*TP53*, 20 (30%) had classic LFS variants (Table 4). Thirty-two individuals (48%) had g*TP53* variants with published evidence of being attenuated (or hypomorphic) variants, and 15 (22%) had variants suggestive of being attenuated (Table 4). Five codons associated with attenuated variants (158, 181, 282, 283, and 337) accounted for 28 of the 67 cases (42%; Fig. 1 and 2, and Supplementary Table 2). Moreover, rare attenuated variants at codon 181 ($n = 10$) were found in all series (except TCGA), and codons 158, 283, and 337 were enriched in four or more series (Supplementary Table 2). Specific *TP53* variants, p.

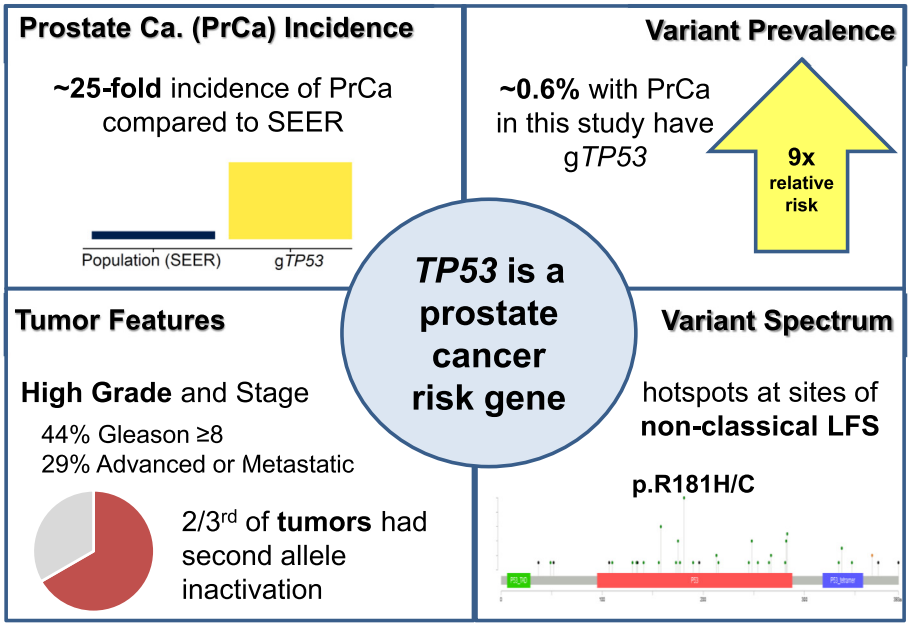


Fig. 1 – Summary of results (graphical abstract). LFS = Li-Fraumeni syndrome; PrCa = prostate cancer; SEER = Surveillance, Epidemiology, and End Results.

Table 2 – Annual prostate cancer incidence rates per 1000 in the Li-Fraumeni syndrome (LFS) and in the Surveillance, Epidemiology, and End Results (SEER) registry

Age (yr)	Restricted LFS cohort [a]		SEER	
	Rate per 1000	95% CI	Rate per 1000	95% CI
0–49	3.9	0.48–14	0.050	0.049–0.050
50–59	40	4.8–144	2.03	2.02–2.04
60–74	90	11–326	7.10	7.08–7.13
0–74	10	3.8–23	1.07	1.07–1.07

CI = confidence interval.
Results are by post hoc age at risk and all ages combined.
[a] LFS cohort restricted to men with no prostate cancer diagnosis at the time of their genetic test.

R158H, p.R181H, p.R282Q, p.R283C, and p.R337H, were each significantly enriched in PrCa cohorts versus gnomAD noncancer controls, with relative risks ranging from 6.1 (for p.R283C) to 92 (for p.R158H; Supplementary Table 4).

3.4. *Tumor analysis in gTP53* carriers supports role in tumorigenesis

As a biallelic loss suggests that the g*TP53* variant contributed to cancer formation, we analyzed available prostate tumors from g*TP53* carriers who had adequate tumor for evaluation. Ten of 15 available tumors (67%), including nine with likely or known attenuated variants, had evidence of somatic inactivation of the second *TP53* allele (Table 4 and Supplementary Table 2). The tumors without evidence of somatic inactivation had either p.R282Q or p.R283C alleles.

3.5. *Clinicopathological features of gTP53* carriers with PrCa

The median age of PrCa diagnosis in males with g*TP53* in this study was 56 (IQR: 51–60) yr (Table 4). PrCa incidence was increased compared with the SEER data in each group analyzed (Table 2 and Supplementary Fig. 2). Of individuals with *gTP53* PrCa in the combined cohorts, 26% had a personal diagnosis and 55% had a family history of an LFS core cancer. Only 26% of the families in the combined cohort did not meet any LFS diagnostic criteria. Nearly all individuals had a family history of cancer, and 30% of patients had a family history of PrCa. A family history of breast cancer was reported in 61% of the combined cohort. Of men with LFS, PrCa was the only or the most recent cancer diagnosis in 58% (18 of 31).

Table 3 – Germline TP53 likely pathogenic/pathogenic variants in prostate cancer (PrCa) cohort compared with the general population

Cohort	Total	LP/P + VUS/LP			ClinVar LP/P		
		n (%)	RR [a] (95% CI)	*p* value	*n* (%)	RR [a] (95% CI)	*p* value
RL	3329	23 (0.69)	11 (7.1–18)	<0.0001	10 (0.30)	11 (5.5–23)	<0.0001
AL-1	831	7 (0.84)	14 (6.4–30)	<0.0001	5 (0.60)	22 (8.7–57)	0.002
AL-2	2191	6 (0.27)	4.5 (2.0–10)	0.0004	1 (0.05)	NA	NA
TCGA	499	2 (0.40)	6.6 (1.6–27)	0.009	0 (NA)	NA	NA
Combined	6850	38 (0.55)	9.1 (6.2–14)	<0.0001	16 (0.23)	8.7 (4.8–16)	<0.0001

AL = Academic Laboratory; CI = confidence interval; RL = reference laboratory; LP/P = likely pathogenic and pathogenic mutations; RR = relative risk; TCGA = The Cancer Genome Atlas; VUS = variants of uncertain significance.
[a] gnomAD v2.1.1 noncancer, 134 187 sample data for *TP53* were downloaded and *TP53* variants classified as LP/P variants as per ClinVar or VUS/LP in ClinVar, classified as likely pathogenic in this study. The rate of LP/P and VUS/LP *TP53* variants in gnomAD was 0.059%, and the rate of ClinVar LP/P *TP53* variants in gnomAD was 0.026%.

Table 4 – Characteristics of 67 PrCa patients with confirmed gTP53

	LFS		PrCa	
	n	%	*n*	%
Site	*n* = 31		*n* = 36	
LFS-1	10	32	–	–
LFS-2	3	10	–	–
LFS-3	6	19	–	
LFS-4	12	39	–	–
RL-1	–	–	7	19
RL-2	–	–	23	64
RL-3	–	–	4	11
TCGA	–	–	2	5.6
Age of PrCa diagnosis	*n* = 31		*n* = 27	
Median (IQR)	56 (50–64)		56 (51–60)	
Mutation class	*n* = 31		*n* = 36	
Classic	12	39	8	22
Reduced penetrance	16	52	16	44
Unknown	3	10	12	33
Tumor LOH	*n* = 6		*n* = 9	
LOH present	6	100	4	44
Personal cancer history	*n* = 31		*n* = 12	
None	11	35	5	42
Sarcoma	8	26	1	8.3
Adrenal cortical tumor	0	–	0	–
Brain	2	6.5	0	–
Leukemia	0	–	0	–
≥1 LFS-core cancer [a]	10	32	1	8.3
Cancer timing for MP	*n* = 19		*n* = 4	
Other cancer after PrCa	7	37	3	75
Other cancer before PrCa	7	37	1	25
Both before and after PrCa	5	26	0	–
Cancer family history	*n* = 31		*n* = 13	
None	1	3.2	1	7.7
Sarcoma	9	29	2	15
Adrenal cortical tumor	3	10	1	7.7
Brain	8	26	5	38
Leukemia	3	10	2	15
Breast age <31	4	13	0	–
Any LFS core cancer [a]	16	52	8	62
Breast (any age)	21	68	6	46
Prostate	9	29	4	31
Clinical LFS criteria	*n* = 28		*n* = 7	
Classic	4	14	1	14
Chompret	13	46	4	57
Birch and/or Eeles	19	68	4	57
No criteria met	8	29	3	43
PrCa Gleason score	*n* = 20		*n* = 14	
GS 6–7	12	60	7	50
GS 8–10	8	40	7	50
PSA at diagnosis	*n* = 14		*n* = 9	
Median (IQR)	6 (4–12)		6 (3–23)	
>20	3	21	3	33
PrCa diagnosis	*n* = 11		*n* = 7	
Screening	8	73	4	57
Incidental	1	9.1	1	14
Symptoms	2	18	2	29
Stage at diagnosis	*n* = 21		*n* = 13	
Localized (Nx or N0)	17	81	7	54
N1 or de novo M1	4	19	6	46

ACT = adrenal cortical tumor; GS = Gleason score; IQR = interquartile range; LFS = Li-Fraumeni syndrome; LOH = loss of heterozygosity; MP = multiple primary; PrCa = prostate cancer; PSA = prostate-specific antigen; RL = reference laboratory; TCGA = The Cancer Genome Atlas.
[a] LFS core cancers: ACT, brain, leukemia, sarcoma, and breast age <31 yr.

Of PrCa cases, 29% were diagnosed as locally advanced (N1) or de novo metastatic disease. Similarly, 44% of g*TP53* individuals had high-grade disease (Gleason ≥8; Fig. 1 and Table 4). Prostate-specific antigen (PSA) at diagnosis ranged from 1.1 to 171 ng/dl, and 68% of individuals were diagnosed by screening. Three individuals were diagnosed due to symptoms of advanced Gleason 9–10 PrCa at ages 50, 51, and 63 yr (Supplementary Table 2).

4. Discussion

We estimate the risk of PrCa diagnosis in individuals with LFS, and the frequency of rare germline pathogenic and likely pathogenic *TP53* variants in a PrCa cohort. We found that LFS men have a 25-fold increased risk of PrCa compared with the general population. Further, we found that 0.55% (range 0.27–0.84%) of individuals with PrCa in a large sequencing cohort have g*TP53*. Tumor sequencing detected second allele inactivation in a majority of available tumor cases, supporting the biological relevance of the g*TP53* variants to tumorigenesis. Collectively, these data demonstrate for the first time that g*TP53* variants contribute to PrCa risk.

There is a paucity of data on PrCa risk in individuals with g*TP53* [8,10]. While an analysis of LFS males in IARC [8] suggested that PrCa was enriched among cancers diagnosed in late adulthood, comparable average ages of cancer onset in LFS patients and SEER population suggested that the contribution of g*TP53* variants was minimal. More recently, Shin et al [6] reported that the incidence of non–LFS-related tumors was higher in male g*TP53* carriers between ages 35 and 65 yr, but PrCa was not analyzed individually. Our findings may differ from prior literature because a larger cohort of older LFS males, including families with attenuated LFS, was included.

Over half of the g*TP53* variants we reported are considered attenuated or hypomorphic variants not typically associated with classic LFS. Individuals with attenuated g*TP53* likely still have a multicancer predisposition syndrome of clinical significance [22,23]. We hypothesize that these individuals are more likely to live into adulthood and be at risk for developing prostate and other adult cancers, compared with those with full-penetrance g*TP53* variants who typically have a severe early-onset cancer phenotype with high mortality rates at young ages.

In the PrCa sequencing cohorts, we found the relative risk of carrying g*TP53* variants to be comparable with that of *BRCA2* (relative risk 4.7–8.6) [24,25], a gene for which PrCa screening recommendations are modified [26,27]. This argues for consideration of PrCa screening in LFS guidelines. Moreover, since g*TP53* carriers may be at an increased risk for radiation-induced sarcomas [5,14], our data may have treatment implications for g*TP53* individuals with PrCa, for example, consideration of MRI versus computed tomography screening and avoidance of therapeutic radiation. The high rate of aggressive disease in our series (29% locally advanced or de novo metastatic) is consistent with prior observations that somatic *TP53* variants are associated with advanced PrCa, and supports the consideration of earlier and/or more frequent screening with PSA and attention to prostate pathology on full-body MRI screening to identify disease at a stage amenable to surgical resection in male g*TP53* carriers from LFS families. For example, one LFS patient in this series had a glioblastoma at age 24 yr, developed symptomatic hematospermia at age 50 yr, and was diagnosed with Gleason score 9 de novo metastatic PrCa, a situation that might have been avoided with screening. In addition, the high rate of other LFS core cancers (61%) and breast cancer at any age (61%) in the family history of the cohort highlights the potential value of cascade familial

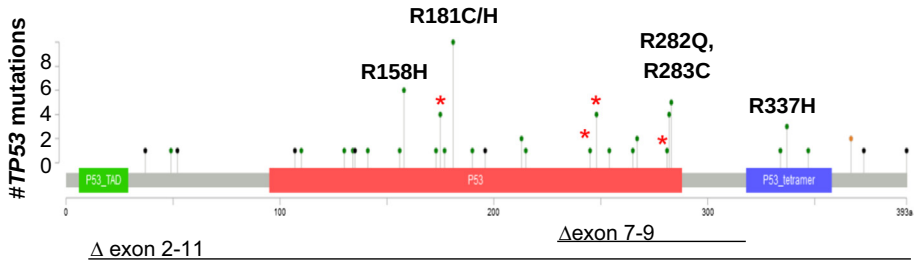


Fig. 2 – Distribution of *TP53* pathogenic and likely pathogenic variants. Lollipop plot depicts 67 germline P/LP variants in patients with prostate cancer. Green color represents missense variants, black represents truncating variants (frameshift, nonsense, and splice site), and black lines represent large deletion variants. Hotspots for prostate cancer were observed at sites of reduced penetrance variants at codons 158, 181, 282, 283, and 337. Classic LFS hotspot variants (R175H, G245S, R248Q, and R282W) are indicated with red asterisks. LFS = Li-Fraumeni syndrome; P/LP = pathogenic and likely pathogenic.

testing to reduce cancer risk in relatives of individuals with PrCa identified to have g*TP53*.

Our study has limitations—the patients represented in all series were ascertained by either clinical testing of PrCa patients or LFS status, and presumably reflect enrichment of family or personal history and younger age. Ascertainment bias is particularly important to consider for the referral laboratory series, which also had very limited clinical data. Part of the increased risk of PrCa diagnosis in the LFS cohort may be due to more frequent testing and biopsy in these men; however, it seems unlikely that this bias could explain the 25-fold increased risk relative to the general US population. In addition, the LFS cohort size is small. However, LFS is an extremely rare cancer syndrome, afflicting approximately one in 10 000–30 000 individuals [28]; therefore, centralized efforts, such as through the LiFE consortium [29], will be required to confirm the risk estimates and clinical correlations presented. It is possible that *TP53*-mutant clonal hematopoiesis of indeterminate potential could contaminate our series [18]; however, paired tumor/normal testing in sequencing cohorts was analyzed, variant allele fraction cutoffs were employed, and LFS males had ancillary tissue or familial testing, proving that the mutation was inherited. Although tumor sequencing results are supportive of mechanistic causality, additional studies would be needed to prove the role in tumorigenesis. Lastly, most individuals did not find out that they were a g*TP53* carrier until after their PrCa diagnosis and could not be utilized in SIR calculations.

Despite these limitations, our complimentary analyses showing an increased incidence of PrCa in an LFS cohort, far higher prevalence of g*TP53* variants in a PrCa cohort than in population controls, tumor data supporting a role in tumorigenesis, and biological plausibility of observing more PrCa in attenuated g*TP53* are collectively compelling. Confirmation in larger numbers of PrCa patients with paired testing of blood and tumor will be helpful, as will better understanding of modifying factors in the context of g*TP53* variants. Exact PrCa risk estimates will likely be specific to variant and population.

5. Conclusions

This study contributes to a greater understanding of *TP53*-associated cancer risk, demonstrating that adult cancers such as PrCa in LFS are understudied and merit further attention. Attenuated or hypomorphic g*TP53* alleles provide a plausible hypothesis as to why some g*TP53* patients develop late adulthood cancers that would not have been appreciated previously in individuals with more severe g*TP53* variants that predispose to high cancer burden and earlier mortality. Screening guidelines for adults with attenuated LFS phenotypes are needed urgently. We suggest that current LFS screening guidelines be updated to consider annual PrCa screening in men with at least 10 yr of life expectancy. While g*TP53* mutation rates are low in PrCa cohorts, the clinical importance of the finding for the patient and family is significant. We suggest evaluation of *TP53* in germline genetic testing in PrCa patients, ideally by paired tumor-normal testing, to rule out somatic interference.

***Author contributions*:** Colin C. Pritchard had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Maxwell, Cheng, Powers, Gulati, Walsh, Pritchard.
Acquisition of data: Maxwell, Cheng, Powers, Ledet, Morrison, Le, Hausler, Stopfer, Hyman, Kohlmann, Naumer, Vagher, Greenberg, Naylor, Laurino, Al-Dubayan, Van Allen, Abida, Carlo, Dubard-Gault, Lee, Maese, Mandelker, Montgomery, Morris, Nicolosi, Nussbaum, Schwartz, Stadler, Garber, Offit, Schiffman, Nelson, Sartor, Walsh, Pritchard.
Analysis and interpretation of data: Maxwell, Cheng, Powers, Gulati, Hausler, Konnick, Shirts, Al-Dubayan, Van Allen, Nguyen, Vijai, Garber, Offit, Walsh, Pritchard.
Drafting of the manuscript: Maxwell, Cheng, Powers, Gulati, Walsh, Pritchard.
Critical revision of the manuscript for important intellectual content: Maxwell, Cheng, Powers, Gulati, Ledet, Morrison, Le, Hausler, Stopfer, Hyman, Kohlmann, Naumer, Vagher, Greenberg, Naylor, Laurino, Konnick, Shirts, Al-Dubayan, Van Allen, Nguyen, Vijai, Abida, Carlo, Dubard-Gault, Lee, Maese, Mandelker, Montgomery, Morris, Nicolosi, Nussbaum, Schwartz, Stadler, Garber, Offit, Schiffman, Nelson, Sartor, Walsh, Pritchard.
Statistical analysis: Maxwell, Cheng, Powers, Gulati, Pritchard.
Obtaining funding: Maxwell, Cheng, Gulati, Garber, Offit, Schiffman, Nelson, Walsh, Pritchard.
Administrative, technical, or material support: None.
Supervision: Garber, Offit, Schiffman, Nelson, Sartor, Walsh, Pritchard.
Other: None.

Financial disclosures: Colin C. Pritchard certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Kara N. Maxwell: no disclosures reported. Heather H. Cheng: research funding to institution from Clovis, Janssen, Sanofi, Medivation/Astellas, and Color Foundation; consultancy to AstraZeneca. Jacquelyn Powers, Roman Gulati, Elisa M. Ledet, Casey Morrison, Anh Le, and Ryan Hausler: no disclosures reported. Jill Stopfer: consultancy to AstraZeneca. Jennie Vagher: consultancy to Invitae. Sophie Hyman, Wendy Kohlmann, Anne Naumer, Samantha Greenberg, Lorraine Naylor, and Mercy Laurino: no disclosures reported. Eric Q. Konnick: travel and honoraria from Roche, Ventana, Medscape, and Clinical Care Options (CCO). Brian H. Shirts and Saud H. Al-Dubayan: no disclosures reported. Eliezer M. Van Allen: consultant/advisory roles from Genome Medical, Invitae, Tango Therapeutics, Manifold Bio, Monte Rosa Therapeutics, and Janssen; research support from BMS and Novartis. Bastien Nguyen and Joseph Vijai: no disclosures reported. Wassim Abida: honoraria from CARET, Roche, Medscape, Aptitude Health, GlaxoSmithKline, Clovis Oncology, and ORIC Pharmaceuticals; consultant for Clovis Oncology, Janssen, MORE Health, ORIC Pharmaceuticals, and Daiichi Sankyo; research funding from AstraZeneca, Zenith Epigenetics, Clovis Oncology, GlaxoSmithKline, ORIC Pharmaceuticals, and Epizyme. Maria Carlo, Marianne Dubard-Gault, and Daniel J. Lee: no disclosures reported. Luke D. Maese: consultant for Jazz Pharmaceuticals. Diana Mandelker, Bruce Montgomery, and Michael J. Morris: no disclosures reported. Piper Nicolosi: employee and shareholder of Invitae Corporation. Robert L. Nussbaum: Employee and shareholder of Invitae Corporation, consultant to Pfizer Pharmaceuticals, consultant and shareholder in Maze Therapeutics and Genome Medical. Lauren E. Schwartz, Zsofia Stadler, Judy E. Garber, and Kenneth Offit: no disclosures reported. Joshua D. Schiffman: employee and shareholder of PEEL Therapeutics. Peter S. Nelson: consultant for Astellas, Janssen, and Bristol Myers Squibb. Oliver Sartor: consultant for Advanced Accelerator Applications, Astellas, AstraZeneca, Bayer Blue Earth Diagnostics Inc., Bavarian, Nordic, Bristol, Myers, Squibb, Clarity, Pharmaceuticals, Clovis, Constellation, Dendreon, EMD, Serono, Fusion, Janssen, Myovant, Myriad, Noria, Therapeutics, Inc., Novartis, Noxopharm, Progenics, POINT, Biopharma, Pfizer, Sanofi, Tenebio, Telix, Theragnostics, Dendreon, Endocyte, Innocrin, Invitae, Merck, and SOTIO; research funding from Advanced Accelerator Applications, AstraZeneca, Bayer, Invitae, and Merck. Michael F. Walsh: no disclosures reported. Colin C. Pritchard: consultant for AstraZeneca.

Funding/Support and role of the sponsor: Research support for this study was generously provided by the National Institutes of Health (K08CA215312, Kara N. Maxwell; R50CA221836, Roman Gulati; R01CA242218, Judy E. Garber; P30CA016520, Abramson Cancer Center; P30CA008748, Memorial Sloan Kettering Cancer Center; P50CA097186, Pacific Northwest Prostate Cancer SPORE, Colin C. Pritchard, Heather H. Cheng, Peter S. Nelson; P30CA015704 FredHutch/UW Cancer Consortium), the Department of Defense (W81XWH-18-1-0756, PC170510, Colin C. Pritchard; W81XWH-18-1-0356, PC170503P2, PC200262P1, Colin C. Pritchard; W81XWH-17-2-0043, Heather H. Cheng; PC200150/W81XWH-21-1-0084, Saud H. AlDubayan; W81XWH-18-1-0406, W81XWH-21-1-0264, Peter S. Nelson), Prostate Cancer Foundation (Kara N. Maxwell, Colin C. Pritchard, Heather H. Cheng, Peter S. Nelson, Saud H. AlDubayan), Burroughs Wellcome Foundation (1017184, Kara N. Maxwell), Basser Center for *BRCA* at the University of Pennsylvania (Kara N. Maxwell), American Society of Clinical Oncology (Saud H. AlDubayan), Breast Cancer Research Foundation (Judy E. Garber, Kenneth Offit), Brotman Baty Institute for Precision Medicine (Brian H. Shirts, Colin C. Pritchard), UW/FHCRC Institute for Prostate Cancer Research (Colin C. Pritchard, Heather H. Cheng, Peter S. Nelson), Niehaus Center for Inherited Cancer Genomics (Michael F. Walsh), Marie-Josée and Henry R. Kravis Center for Molecular Oncology (Michael F. Walsh), Elephant p53 (EP53) Program and its generous funding provided to Huntsman Cancer Institute by the State of Utah (Joshua D. Schiffman), 5 For The Fight (Joshua D. Schiffman), Soccer for Hope Foundation (Joshua D. Schiffman), and Li-Fraumeni Syndrome Association (Joshua D. Schiffman).

***Acknowledgments*:** We thank the UW Genetics and Solid Tumors Laboratory and NGS Analytics Lab for support with genetic testing and data analysis.

Peer Review Summary

Peer Review Summary associated with this article can be found online version, at https://doi.org/10.1016/j.eururo.2021.10.036.

References

[1] Eeles R, Goh C, Castro E, et al. The genetic epidemiology of prostate cancer and its clinical implications. Nat Rev Urol 2014;11:18–31.
[2] Nicolosi P, Ledet E, Yang S, et al. Prevalence of germline variants in prostate cancer and implications for current genetic testing guidelines. JAMA Oncol 2019;5:523–8.
[3] Pritchard CC, Mateo J, Walsh MF, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med 2016;375:443–53.
[4] Malkin D, Li FP, Strong LC, et al. Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. Science 1990;250:1233–8.
[5] Bougeard G, Renaux-Petel M, Flaman JM, et al. Revisiting Li-Fraumeni syndrome from TP53 mutation carriers. J Clin Oncol 2015;33:2345–52.
[6] Shin SJ, Dodd-Eaton EB, Peng G, et al. Penetrance of different cancer types in families with Li-Fraumeni syndrome: a validation study using multicenter cohorts. Cancer Res 2020;80:354–60.
[7] Mai PL, Best AF, Peters JA, et al. Risks of first and subsequent cancers among TP53 mutation carriers in the National Cancer Institute Li-Fraumeni syndrome cohort. Cancer 2016;122:3673–81.
[8] Amadou A, Waddington Achatz MI, Hainaut P. Revisiting tumor patterns and penetrance in germline TP53 mutation carriers: temporal phases of Li-Fraumeni syndrome. Curr Opin Oncol 2018;30:23–9.
[9] Rana HQ, Gelman R, LaDuca H, et al. Differences in TP53 mutation carrier phenotypes emerge from panel-based testing. J Natl Cancer Inst 2018;110:863–70.
[10] Spees CK, Kelleher KJ, Abaza R, Clinton SK. Prostate cancer and Li-Fraumeni syndrome: implications for screening and therapy. Urol Case Rep 2015;3:21–3.
[11] Siegel DA, O'Neil ME, Richards TB, Dowling NF, Weir HK. Prostate cancer incidence and survival, by stage and race/ethnicity—United States, 2001–2017. MMWR Morb Mortal Wkly Rep 2020;69:1473–80.
[12] Kratz CP, Achatz MI, Brugieres L, et al. Cancer screening recommendations for individuals with Li-Fraumeni syndrome. Clin Cancer Res 2017;23:e38–45.
[13] Frebourg T, Bajalica Lagercrantz S, Oliveira C, Magenheim R, Evans DG. European Reference Network GENTURIS. Guidelines for the Li-Fraumeni and heritable TP53-related cancer syndromes. Eur J Hum Genet 2020;28:1379–86.
[14] Heymann S, Delaloge S, Rahal A, et al. Radio-induced malignancies after breast cancer postoperative radiotherapy in patients with Li-Fraumeni syndrome. Radiat Oncol 2010;5:104.
[15] Hendrickson PG, Luo Y, Kohlmann W, et al. Radiation therapy and secondary malignancy in Li-Fraumeni syndrome: a hereditary cancer registry study. Cancer Med 2020;9:7954–63.
[16] Landrum MJ, Lee JM, Benson M, et al. ClinVar: improving access to variant interpretations and supporting evidence. Nucleic Acids Res 2018;46:D1062–7.
[17] Fortuno C, Lee K, Olivier M, et al. Specifications of the ACMG/AMP variant interpretation guidelines for germline TP53 variants. Hum Mutat 2021;42:223–36.

[18] Weitzel JN, Caho EC, Nehoray B, et al. Somatic TP53 variants frequently confound germline testing results. Genet Med 2018;20:809–16.
[19] Cheng DT, Mitchell TN, Zehir A, et al. Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT): a hybridization capture-based next-generation sequencing clinical assay for solid tumor molecular oncology. J Mol Diagn 2015;17:251–64.
[20] Pritchard CC, Salipante SJ, Koehler K, et al. Validation and implementation of targeted capture and sequencing for the detection of actionable mutation, copy number variation, and gene rearrangement in clinical cancer specimens. J Mol Diagn 2014;16:56–67.
[21] Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Control Clin Trials 1996;17:343–6.
[22] Powers J, Pinto EM, Barnoud T, et al. A rare TP53 mutation predominant in Ashkenazi Jews confers risk of multiple cancers. Cancer Res 2020;80:3732–44.
[23] Mastellaro MJ, Seidinger AL, Kang G, et al. Contribution of the TP53 R337H mutation to the cancer burden in southern Brazil: insights from the study of 55 families of children with adrenocortical tumors. Cancer 2017;123:3150–8.
[24] Breast Cancer Linkage Consortium. Cancer risks in BRCA2 mutation carriers. J Natl Cancer Inst 1999;91:1310–6.
[25] Lecarpentier J, Silvestri V, Kuchenbaecker KB, et al. Prediction of breast and prostate cancer risks in male BRCA1 and BRCA2 mutation carriers using polygenic risk scores. J Clin Oncol 2017;35:2240–50.
[26] NCCN. NCCN guidelines version 1.2019. Prostate cancer early detection.
[27] Giri VN, Knudsen KE, Kelly WK, et al. Implementation of germline testing for prostate cancer: Philadelphia Prostate Cancer Consensus Conference 2019. J Clin Oncol 2020;38:2798–811.
[28] MacFarland SP, Zelley K, Long JM, et al. Earlier colorectal cancer screening may be necessary in patients with Li-Fraumeni syndrome. Gastroenterology 2019;156:273–4.
[29] Mai PL, Sand SR, Saha N, et al. Li-Fraumeni Exploration Consortium Data Coordinating Center: building an interactive web-based resource for collaborative international cancer epidemiology research for a rare condition. Cancer Epidemiol Biomarkers Prev 2020;29:927–35.

REVIEW ARTICLE

Disparities in germline testing among racial minorities with prostate cancer

Nicole Weise[1], Justin Shaya[1], Juan Javier-Desloges[1], Heather H. Cheng[2,3], Lisa Madlensky[1] and Rana R. McKay[1]✉

Germline testing is becoming increasingly relevant in prostate cancer (PCa) screening, prognosis, and management. A subset of patients with PCa harbor pathogenic/likely pathogenic variants (P/LPVs) in genes mediating DNA-repair processes, and these P/LPVs have implications for cancer screening, treatment, and cascade testing. As a result, it is recommended that all men with high-risk localized and metastatic PCa undergo routine germline testing. As more PCa patients undergo germline testing, it is important that clinicians and genetics experts recognize current disparities in germline testing rates among racial/ethnic minorities in the United States. The reasons for these disparities are multiple and require similarly manifold consideration to close the germline testing gap and reduce inequities in PCa screening, management, and treatment.

Prostate Cancer and Prostatic Diseases; https://doi.org/10.1038/s41391-021-00469-3

INTRODUCTION

Prostate cancer (PCa) is the most common cancer among men and one of the leading causes of deaths worldwide [1]. In 2021, it is estimated that 248,530 men in the United States (US) will be diagnosed with PCa and 34,130 individuals will die secondary to this disease [2]. While age, race/ethnicity, and family history are established risk factors for PCa, it is now recognized that a proportion of PCa susceptibility is attributed to genetic predisposition. Advances in molecular sequencing technologies have identified several PCa susceptibility genes, many related to known hereditary cancer syndromes, including hereditary breast and ovarian cancer (HBOC) syndrome (*BRCA1*, *BRCA2*, *ATM*, *CHEK2*, and *PALB2*) and Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) [3]. As a result of these findings, recommendations for germline testing based on clinical features and family history have expanded. The identification of pathogenic/likely pathogenic variants (P/LPVs) in PCa predisposition genes may help inform cancer screening strategies for patients and family members, treatment options in the metastatic setting, and clinical trial enrollment.

As germline testing becomes more clinically relevant and widely available, it is important to recognize the risk of exacerbating health disparities among racial/ethnic minorities with PCa and develop systematic strategies to bridge disparities in germline testing. Reasons for these disparities are multifaceted and include patient, clinician, and system factors. Additionally, current PCa clinical trials and genetic studies do not reflect the diverse populations of individuals at-risk or suffering from this disease. In this review, we discuss the indications for germline testing in men with PCa, barriers to germline testing in diverse populations, and potential strategies to bridge the disparities gap with the expansion of germline testing for men with PCa.

DISPARITIES IN OUTCOMES OF MEN WITH PCA

There are documented disparities in the incidence, treatment, and mortality of PCa between Black and non-Black men [2, 4–6]. Notably, Black men are diagnosed with PCa at nearly twice the rate of non-Hispanic white (NHW) men [2], and Black men with local/regional PCa have been found to be less likely to receive treatment with curative intent than NHW men [7]. Further, the PCa mortality rate is twice as high in Black men compared to NHW men [2]. The National Cancer Institute estimates that Black men have a 4.72% lifetime risk of dying of PCa compared to a 2.86% risk among NHW men [5]. Although biological differences may account for a portion of the disparity in overall PCa survival, it has been suggested that improved access to care, including screening, follow-up, and therapy may be effective in reducing this disparity [8]. It is important to note that one limitation of studies of PCa incidence and mortality is that most data on Black men does not stratify them by country/region of origin—Black men are not a homogenous group and there may be differences in PCa incidence and mortality for Caribbean, African, and African-American men [9].

Similarly, despite the genetic and cultural diversity of Hispanic men in the US, individual subgroups are typically combined. Notably, significant heterogeneity has been observed among Hispanic men with PCa [10]. Overall, PCa occurs less often in Hispanic men than in NHW men [1]. However, Mexican-American men have been found to have more advanced stage PCa at diagnosis [11] and are significantly more likely to have aggressive PCa following radical prostatectomy [12]. While prostate cancer-specific mortality (PCSM) is comparable between Hispanic and NHW men, Puerto Rican men have been shown to have significantly higher PCSM than NHW men, Black men, and all

[1]University of California San Diego, San Diego, CA, USA. [2]University of Washington, Seattle, WA, USA. [3]Fred Hutchinson Cancer Research Center, Seattle, WA, USA. ✉email: rmckay@ucsd.edu

Received: 4 September 2021 Revised: 27 October 2021 Accepted: 2 November 2021
Published online: 13 November 2021

Table 1. Representation of diverse racial/ethnic groups in prostate cancer clinical trials involving germline testing.

Trial	Race					Ethnicity (Hispanic or Latino)		
	N	White	Black	Asian	Other/Unknown	No	Yes	Unknown
Metastatic Hormone Sensitive Prostate Cancer								
CHAARTED—Docetaxel [72]	790	674	76	NR	40	NR	NR	NR
STAMPEDE—Docetaxel [73]	2962	NR	NR	NR	NR	NR	NR	NR
LATITUDE—Abiraterone [74]	1199	NR	NR	NR	NR	NR	NR	NR
STAMPEDE—Abiraterone [75]	1917	NR	NR	NR	NR	NR	NR	NR
TITAN—Apalutamide [76]	1052	719	19	229	85	NR	NR	NR
ARCHES—Enzalutamide [77]	1150	926	16	155	53	NR	NR	NR
ENZAMET—Enzalutamide [78]	1125	NR	NR	NR	NR	NR	NR	NR
MCRPC								
TAX 327—Docetaxel [79]	1006	NR	NR	NR	NR	NR	NR	NR
TROPIC—Cabazitaxel [80]	755	631	40	58	26	NR	NR	NR
IMPACT—Sipuleucel-T [81]	512	461	30	NR	21	NR	NR	NR
ALSYMPCA—Radium-223 [82]	921	865	NR	NR	NR	NR	NR	NR
COU-AA-301—Abiraterone post-chemo [83]	1195	NR	NR	NR	NR	NR	NR	NR
COU-AA-302—Abiraterone pre-chemo [84]	1088	NR	NR	NR	NR	NR	NR	NR
AFFIRM—Enzalutamide post-chemo [85]	1199	NR	NR	NR	NR	NR	NR	NR
PREVAIL—Enzalutamide pre-chemo [86]	1717	1324	34	167	192	1527	38	152
NMCRPC								
SPARTAN—Apalutamide [87]	1200	800	68	140	192	NR	NR	NR
PROSPER—Enzalutamide [88]	1401	NR	NR	NR	NR	NR	NR	NR
ARAMIS—Darolutamide [89]	1509	NR	NR	NR	NR	NR	NR	NR

MCRPC metastatic castration-resistant prostate cancer, *NMCRPC* non-metastatic castration-resistant prostate cancer, *NR* not reported.

other Hispanic subgroups [10]. Ultimately, the dearth of PCa studies examining individual Hispanic subgroups makes it difficult to compare them to NHW men.

Despite these documented disparities, African-American/Canadian, Asian/Pacific Islander, and Hispanic populations are typically underrepresented in germline testing, clinical trials (Table 1), and study cohorts [13]. One study analyzed 72 global phase III and IV prevention, screening, and treatment PCa clinical trials between 1987 and 2016: 59 trials reported race/ethnicity data, and 96% of patients enrolled in these studies were NHW men. African and Caribbean medical centers were particularly underrepresented in these trials [14]. Concordant studies have shown that the majority of PCa patients receiving germline testing are NHW men [15, 16], with as high as 95% being English-speaking men [16]. Underrepresentation of racial/ethnic minorities in germline testing is not unique to PCa and exists among patients with various other malignancies [17–19].

Racial/ethnic minority populations in the US are expected to grow rapidly over the coming decades, underscoring the need to address and resolve these disparities. It is projected that by 2045, NHW people will make up <50% of the total US population. While NHW populations are expected to decline, all other racial/ethnic minority populations are expected to grow: in particular, Hispanic populations are the fastest growing demographic and are expected to comprise 24.6% of the US population in 2045, up from 18.7% in 2020 [20].

GENOMICS OF NON-WHITE MEN WITH PCA

P/LPVs have been found to be prevalent in men with PCa. A 2016 multi-institutional study found that the incidence of germline mutations in genes mediating DNA-repair processes (including but not limited to *BRCA2*, *ATM*, *CHEK2*, *BRCA1*, *RAD51D*, and *PALB2*) among 692 men with metastatic PCa was 11.8% [3]. For patients with localized disease, the prevalence of P/LPVs ranged from 2 to 6%, with increased prevalence in men with higher Gleason scores and higher-risk PCa. Notably, 576 (83%) of the men in this study were NHW men. Additionally, a 2021 study found that 9.5% of PCa patients with high-risk localized disease had P/LPVs, most frequently in *BRCA2* and *ATM* [21].

In order to better understand the genomic landscape of racial/ethnic minorities, there is a need to more extensively examine P/LPV rates in non-white men with PCa. More recent studies have found that the prevalence of P/LPVs varies across racial/ethnic groups. When compared to NHW men, Hispanic men with PCa have been found to have similar rates of P/LPVs in the *ATM*, *BRCA1*, and *BRCA2* genes [22], while Black men with PCa have been found more likely to have a P/LPV in the *BRCA1* gene than their NHW counterparts [23]. Among patients with metastatic PCa, mutations in DNA-repair genes have been found to occur more often in Black men than in NHW men [24]. However, these studies were limited by small sample size.

The lack of diversity in germline testing cohorts is thought to be a contributor to higher rates of variants of uncertain significance (VUS) in racial/ethnic minorities [15, 25]. Notably, African-American, Hispanic, and Asian/Pacific Islander PCa patients have been found to be more likely to have a VUS than those with European ancestry [23, 26]. In one study of PCa patients referred to Color Genomics for germline testing, VUS rates in HBOC and Lynch syndrome genes were 21% in NHW men, while 26.6% and 33.3% in African-American/Canadian and Asian/Pacific Islander men, respectively [15]. Increasing the proportion of underrepresented groups in germline testing cohorts is predicted to result in the reclassification of VUS, which will assist in cancer risk stratification and targeted therapy strategies [15].

Table 2. Guidelines on germline testing in prostate cancer.

Source	Regional (N1)/ metastatic prostate cancer	NCCN very high and high-risk localized prostate cancer	NCCN intermediate/low/very low risk localized prostate cancer
National Comprehensive Cancer Network Version 1.2022 [27, 28]	Recommend	Recommend	Recommend if a family history of: • Ashkenazi Jewish ancestry • High-risk germline mutations (e.g., *BRCA1/2*, Lynch mutation) • PCa in brother/father/multiple family members diagnosed with PCa (not GG1) at <60 years of age or who died from PCa • ≥3 cancers on same side of family, especially diagnoses ≤50 years of age: bile duct, breast, colorectal, endometrial, gastric, kidney, melanoma, ovarian, pancreatic, prostate (not GG1), small bowel, or urothelial cancer Consider for: Intraductal/cribriform histology
Philadelphia Prostate Cancer Consensus Meeting Publication 2019 [90]	Recommend	• Consider for T3a or higher. • Consider for intraductal/ductal pathology. • Consider for Gleason 4 (Gleason 8 sum) or above. • Consider for Ashkenazi Jewish ancestry. • Consider for family history of two or more cancers in HBOC/Lynch spectrum in any relatives on the same side of the family (especially if diagnosed at age <50 years). • Recommend for family history of one brother/father/two or more male relatives with one of the following: • PCa at age <60 years • Died of PCa. • Metastatic PCa.	
AUA/ASTRO/SUO 2017 and 2021 [91–93]	Recommend	Recommend if a strong family history of specific cancers (e.g., breast, ovarian, pancreatic, other gastrointestinal tumors, and lymphoma).	Not recommended

PCa Prostate Cancer, *HBOC* Hereditary Breast and Ovarian Cancer Syndrome, *NCCN* National Comprehensive Network, *AUA* American Urological Association, *ASTRO* American Society of Radiation Oncology, *SUO* Society of Urologic Oncology, *GG* Grade Group.

INDICATIONS FOR GERMLINE TESTING AND IMPLICATIONS OF TESTING RESULTS

Recent studies on the incidence of P/LPVs among men with PCa have resulted in updated guidance regarding which patients should receive germline testing. The most recent iteration of the National Comprehensive Cancer Network guidelines for PCa recommends germline testing for all men with high-risk localized and metastatic PCa, Ashkenazi Jewish ancestry, a family history of high-risk germline mutations, or a positive family history of cancer [27, 28]. Given emerging data on the association between intraductal/cribriform and ductal histologies and P/LPVs, testing is considered for men with these histologic subtypes [28]. Other professional societies and expert panels have also provided recommendations for germline testing for men with PCa, largely based on evidence synthesis, consensus agreement, and expert opinion (Table 2).

Expanding germline testing uptake may help clinicians predict outcomes in men with PCa by detecting ethnicity-dependent biomarkers and mutations that drive aggressive tumor biology [29]. Germline mutations in DNA-repair genes, particularly *BRCA1/2* and *ATM*, are associated with aggressive PCa and significantly shorter survival time: mutation carriers have been found to have a higher proportion of Gleason Score ≥7 (71%) than noncarriers (31%) and mutation frequency has been found to be significantly higher in patients that have died of PCa than in localized PCa patients [30].

Germline testing also has implications regarding candidacy of select treatments, including platinum chemotherapy, poly(ADP-ribose) polymerase (PARP) inhibitors, and checkpoint inhibition for patients with metastatic castration-resistant prostate cancer (mCRPC) [31]. In 2020, the PARP inhibitor Olaparib was FDA approved for the treatment of adult patients with deleterious/suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated mCRPC who have progressed following prior treatment with enzalutamide or abiraterone. Olaparib is FDA approved for a panel of 14 genes, including *BRCA1/2*. Of the patients in the PROfound trial, 69% were white, 29% were Asian, and 1% were Black [32]. Another therapy, Rucaparib, was FDA approved in 2020 for the treatment of adult patients with a deleterious *BRCA1/2* mutation (germline and/or somatic)-associated mCRPC who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy. For the 115 patients enrolled in the TRITON2 study, the majority were white (73%) and 10% were Black; other racial/ethnic groups were not specified [33]. Pembrolizumab has also been FDA approved for patients with refractory metastatic cancers with MSI-high or MMR deficiency (dMMR) status based on tumor assessment that had progressed following prior treatments [34]. Pembrolizumab has shown antitumor activity with an acceptable safety profile in an unselected subset of patients with mCRPC [35].

Another indication for germline testing is cascade testing, which refers to germline testing among relatives of patients with cancer-associated P/LPVs; it has historically had decreased uptake in the community at around 30% or less. Being a PCa patient with a germline P/LPV in a DNA-repair gene has been associated with having a first degree relative with breast or ovarian cancer [36]. Therefore, increased germline testing among PCa patients may result in increased cascade testing for family members and subsequent breast and ovarian cancer risk mitigation.

Table 3. Challenges and solutions.

Challenges	Solutions
Shortage of CGCs and limitations of current GC models	• Increase clinical training capacity for CGCs • Offer pretest GC and select posttest GC via alternative methods (telemedicine, group GC) • Automate risk assessment
Differences in the quality of care for minority patients	• Increase access to genetic services, contain costs, and address provider implicit bias
Medical mistrust	• System wide interventions to address gaps in healthcare delivery • Increase representation of minorities in healthcare • Community outreach
Lack of knowledge regarding testing	• Increase genetics education among patients and community health providers • Culturally tailored genetic counseling
Prohibitive cost and lack of insurance coverage for germline testing	• Increase payer coverage • Low-cost testing and government subsidies
Understudied link between PCa and breast/ovarian cancers	• Address similar disparities in germline testing among women with HBOC syndrome • Physician and patient directed education regarding genetic link between PCa and HBOC syndrome

CGC Clinical Genetic Counselor, *GC* Genetic Counseling, *PCa* Prostate Cancer, *HBOC* syndrome Hereditary Breast and Ovarian Cancer Syndrome.

REASONS FOR THE DISPARITIES IN GERMLINE TESTING AMONG RACIAL/ETHNIC MINORITIES WITH PCA AND POTENTIAL STRATEGIES TO BRIDGE THE GAP

Although germline testing is now routinely recommended for high-risk localized, locally advanced, and metastatic PCa patients, there is a disparity in the proportion of white vs. non-white PCa patients receiving germline testing [15, 16, 26]. We propose several reasons and potential solutions for this disparity, including the (1) nationwide shortage of genetic counselors to facilitate germline testing within current genetic counseling models, (2) differences in access to quality healthcare between white and non-white patients, (3) healthcare system mistrust among non-white men leading to unfavorable attitudes towards research and reluctance to seek care, (4) lack of knowledge or education about germline testing, (5) prohibitive cost of germline testing, and (6) understudied link between PCa and breast/ovarian cancer (Table 3).

Challenge and solution: shortage of genetic counselors and limitations of current genetic counseling models

Certified Genetic Counselors (CGCs) and physicians work cooperatively to facilitate germline testing and provide counseling, risk assessment, and result interpretation to PCa patients. The shortage of clinical cancer CGCs engaged in direct patient care creates an unmet need for genetic services that disproportionately affects socioeconomically disadvantaged, rural, and racial/ethnic minority patients. As the demand for germline testing grows, CGC workforce growth limitations will need to be addressed. One such limitation is clinical training capacity. Proposed solutions include novel clinical training techniques, such as nonclinical or extra-disciplinary training placements, rural clinical placements, peer supervision/assisted learning, role-emerging placements, clinical audit, and patient simulation. Perhaps most important is the need to recruit, train, and retain clinical supervisors by providing dedicated support personnel and professional development opportunities [37].

In addition to a nationwide shortage of CGCs engaged in direct patient care, existing genetic counseling models are becoming increasingly inadequate given the number of PCa patients referred for germline testing. The current time-intensive model of assessing family histories for genetic risk, providing pretest and posttest counseling, ordering appropriate testing, and interpreting test results over multiple in-person sessions is increasingly less feasible. Increased genetic literacy among medical oncologists, urologists, and radiation oncologists, including knowledge of patient risk factors and family history, genetics and genetic conditions, and available genetic services, may alleviate bottlenecks at the genetic counseling level [38].

Modifications to existing workflows within oncology practices may expand genetic resources for patients. Automating the risk assessment would be one such modification, whereby patient-completed family history questionnaires facilitate referral and testing processes: automated electronic medical record features can trigger genetic counseling referrals or alert clinical teams to patients with elevated cancer risks or who meet guidelines for germline testing. This would allow CGCs to prioritize posttest visits, especially those involving complex counseling or abnormal results [39]. Other practical strategies focus on increasing CGC efficiency and patient volumes, including group genetic counseling sessions. Additionally, establishing support roles, such as genetic counseling assistants, can alleviate administrative burdens [8]. Likewise, patient advocates and language interpreters in the genetic counseling setting can provide resources and translation services for non-English-speaking patients, which would further alleviate burdens on monolingual English-speaking CGCs and reduce patient miscommunication.

Rural patients are particularly disadvantaged by current genetic counseling models, given the scarcity of CGCs in more rural counties and among populations with a low median household income [40]. Telemedicine, which has been adopted by many clinics in the COVID-19 era [41], can help bridge this gap: video genetics education and genetic counseling may be as effective as traditional genetic counseling and has resulted in a similar uptake of germline testing without compromising the tenants of informed consent [42]. Telemedicine models do, however, need to adapt to potential challenges, including limited internet access, scheduling issues, billing questions, and state licensure regulations [41].

Challenge and solution: differences in the quality of care between white and non-white patients

There is overwhelming evidence that there are disparities in the quality of healthcare between white and non-white patients, even when insurance status, income, age, and severity of conditions are comparable [43]. Significant disparities have been noted for definitive therapy for PCa [6], with Black men being particularly underrepresented in PCa research, including validation studies of new clinical tools like genomic testing [15, 44]. One explanation

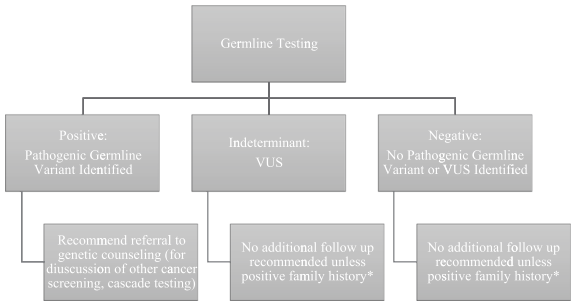


Fig. 1 Post-germline testing workflow depending on test result [27, 28]. VUS Variant of uncertain significance. *Genetic counseling recommended to discuss possible participation in family studies and variant reclassification studies.

for this disparity is that minority-serving physicians have been found to be significantly less likely to have ever referred a patient for germline testing or counseling, specialty services, or clinical trials [45]. This may be the result of many underlying issues, including access and cost.

Strategies to integrate genetic services into minority community health settings will be critical in ensuring the accessibility of germline testing. Because most CGCs are concentrated within large academic medical centers and hospital systems, the incorporation of satellite campuses and clinics into medically underserved communities would greatly expand access. In tandem, minority community health programs can practice evidence based medicine through the implementation of clinical pathways to ensure that all patients are receiving the minimum standard of care. This will require expanding physician knowledge and awareness of current PCa clinical practice guidelines, as well as integration of these guidelines into existing workflows (Fig. 1).

Despite the expansion of germline testing guidelines for PCa patients, germline testing is not routinely covered by insurance. Coverage policies for germline testing in PCa patients are nonspecific and nonuniform across insurance companies, and physicians may not recommend genetic services for patients who cannot afford the out-of-pocket costs [46]. Expanding insurance coverage to include PCa patients that meet recommendations for germline testing may alleviate cost barriers. Additionally, in the absence of genetic services in medically underserved communities, expanded insurance coverage for transportation costs may benefit those who cannot access such services due to geographic barriers and for whom in-person counseling may help overcome hesitation due to unfamiliarity with telemedicine and/or lack of trust in the healthcare system.

Challenge and solution: medical mistrust leading to unfavorable attitudes towards research and medicine

Healthcare disparities among racial/ethnic minorities are thought to contribute to long-standing generational mistrust in healthcare-providing entities in the US. Medical mistrust has been shown to lower utilization of routine checkups and preventive care services [47–49], including referrals for genetic counseling and testing. Delays in these services may prevent a substantial number of men from obtaining recommended services until an advanced stage of illness [47]. This mistrust becomes a barrier to an emphasis on prostate health [50] and precludes racial/ethnic minorities from seeking PCa screening, germline testing, and treatment.

The lack of representation within medical institutions, as well as subsequent language barriers, may be a contributor to medical mistrust. In 2019, 5.0% and 5.8% of physicians identified as Black and Hispanic, respectively [51]. Further, 10.0% of CGCs in the US identified as non-white in 2021 [52]. Representation improves patient-clinician communication and rapport: when provided a doctor of the same race, Black men have been found be more likely consent to invasive services, such as blood draws and biopsies, and discuss personal matters or health issues [53]. Hispanic men, in contrast, may face language barriers with clinicians: monolingual English-speaking clinicians may have limited communication with patients or rely on interpreters or translated materials, which may convey confusing or even contradictory information [54]. Issues of representation can be addressed by actively recruiting racial/ethnic minorities to the healthcare workforce and creating student training programs targeting these populations [55]. Language challenges can be addressed by employing multilingual, culturally cognizant interpreters in clinics where the need exists [56].

Medical mistrust may also stem from implicit bias, which refers to the unconscious and unintentional attitudes and stereotypes attributed towards a group of people. Implicit bias may contribute to health disparities by shaping physician behavior and producing differences in treatment along the lines of race, ethnicity, and gender. Healthcare professionals can combat implicit bias by individuating, which involves a conscious focus on specific information about a patient instead of their race, ethnicity, or gender [57]. Addressing implicit bias early is essential: genetic counseling and nursing programs, medical schools, and healthcare professional training programs can expand and emphasize coursework in racial sensitivity and implicit bias. Additionally, addressing implicit bias in continuing medical education may help minimize biases.

Medical mistrust may also result from a lack of trust regarding the use of genetic information. Despite the passage of the Genetic Information Nondiscrimination Act in 2008, which was designed to protect Americans against discrimination in health insurance and employment based on their genetic information [58], utilization of genetic services among racial/ethnic minorities is disproportionately low [59]. In response, providers need to anticipate and dispel patient fears about germline testing. Patients may believe that their results are not confidential or that positive results will leave them susceptible to discrimination, reduced access to care, or insurance coverage loss [44]. Patients may also conflate germline testing ordered by a clinician with direct-to-consumer DNA testing provided by companies that have faced controversy for sharing customers' data with law enforcement and pharmaceutical companies.

Outreach and community support may help combat medical mistrust. Distributing medical literature directly to underserved populations has been shown to have positive results; however, personalized interactions between clinicians and racial/ethnic minority communities may further build trust and assuage fears about genetic services in order to encourage participation in germline testing and clinical trials [59]. Outreach and educational efforts within community institutions (such as churches) that involve partners and spouses, as well as cancer survivors within the community, may play a pivotal role [60].

Challenge and solution: lack of knowledge regarding testing

A lack of knowledge regarding germline testing and its implications for PCa screening, diagnostics, and treatment may present further barriers [38]. The availability of reliable, easy-to-understand information regarding the effects of P/LPVs on disease, as well as the importance of personal or family history of disease, is crucial [56].

Access to clear, concise tools about genetics is important because the complexity of such tools may compromise their effectiveness in identifying individuals at-risk for PCa. Genetics education among the general public is also important because individuals who are aware of and ask for specialized genetic services are the most likely to receive them [25]. Clear, simple, prescriptive education on genetics needs to be widely available to all PCa patients, and physicians will need to communicate the

advantages of genetic counseling and germline testing when they encounter high-risk localized and metastatic PCa patients who may benefit from it [40].

A lack of cross-cultural communication may also prevent racial/ethnic minorities from seeking or consenting to germline testing. The cultural impact of cancer can have an effect on patients' attitudes towards germline testing: some South Asian and African-American communities have been found to take on a fatalistic view of cancer, associating the diagnosis with death; they may not wish to pursue testing if they believe nothing can be done to prevent or treat it [61]. Culture can also have an effect on the acceptance of test results: patients who receive germline testing may fear that their results will ostracize them from their family or community. Additionally, patients may not understand what a positive, negative, or inconclusive result means in the context of their own health and their family's health. One solution could be culturally tailored genetic counseling (CTGC) and testing programs, which have been developed and evaluated to improve access to risk assessment services, subsequently enhancing the quality of care among patients from racial/ethnic minority groups. CTGC consists of education about risk factors for hereditary disease, personalized risk information, and discussions about the benefits, limitations, and risks of germline testing [56].

Challenge and Solution: prohibitive cost and lack of insurance coverage for germline testing

Access to germline testing is often limited by access to quality, affordable health insurance, which varies by race/ethnicity: NHW people are more likely to have health insurance than racial/ethnic minorities [62]. Additionally, NHW people are more likely to have private health coverage as opposed to public health coverage, such as Medicare and Medicaid [62]. Patients who are uninsured, underinsured, or insured by government programs may face significant barriers to obtaining care—for example, they may be denied care by private physicians, leading them to seek care in emergency departments, public hospital systems, or local health departments which may not offer the same referrals or specialty and preventative services as private practices [63]. Overall, having health insurance is strongly associated with undergoing PCa screening, lower stage of cancer at diagnosis, treatment for local/regional disease, prostatectomy, PCa survival, and quality of life [5]. Without health insurance, the cost of germline testing is often prohibitive. And, even when germline testing is covered by insurance, there may be prohibitive out-of-pocket costs, including deductibles and copayments. Additionally, not all insurers cover germline testing for PCa [46], including some private insurers and public options such as Medicare and Medicaid [64].

There are programs that increase PCa patient access to genetic services by offering free or reduced cost germline testing. Color Genomics offers a relatively low-cost risk analysis of several genes associated with PCa, as well as access to CGC and physician services [65]. Additionally, Invitae offers free germline testing and counseling for hereditary PCa through their Detect Hereditary Prostate Cancer program, in which eligible patients work with a genetic counselor or physician to order testing [66]. These, along with research studies such as the patient-driven PROMISE registry, which offers medical Color Genomics germline testing by mail to men with any stage of PCa [67], can reduce cost and access barriers.

Additional strategies for increasing payer coverage for germline testing and reducing test costs are necessary in order to create equitable access for all PCa patients. Strategies to increase insurance coverage may include clarifying and expanding Current Procedural Terminology codes to allow coverage for more specific tests and adding genetic specialists to insurance company staff to address shortages of genetic expertise. To address the costs of genetic tests, government subsidy programs and cost caps may be helpful in mitigating the cost to both the patient and insurers. Ultimately, there is a need for healthcare coverage reform in the US. In the absence of publicly funded healthcare, improving provider discussions about out-of-pocket costs is critical for ensuring informed patient testing and treatment decisions [64].

Challenge and solution: understudied link between PCa and breast/ovarian cancers

P/LPVs of *BRCA1/2* have been found to increase the risk of multiple cancers, including those of the breast, ovary, and prostate. These P/LPVs have clinical implications for PCa patients as well as their families. *BRCA1/2* associated HBOC should be suspected in individuals with family history of PCa and other cancers associated with HBOC syndrome [68], and likewise, PCa risk should be considered in individuals with a personal history of male breast cancer and/or family history suggestive of HBOC syndrome [69].

As with PCa, there are disparities in germline testing rates among racial/ethnic minority women with HBOC syndrome. These disparities are thought to be a result of multiple factors, including medical mistrust and fears of discrimination on the basis of genetic information [70]. Such disparities are thought to contribute to concordant disparities among racial/ethnic minority men with PCa. Therefore, addressing germline testing disparities among women with HBOC syndrome may aid in identifying male family members at-risk for developing PCa, as well as those already diagnosed with PCa who would benefit from germline testing's impact on treatment options.

One particular challenge for PCa patients is that the names of certain PCa predisposition genes and familial risk factors (e.g., *BRCA1/2* and HBOC syndrome) do not make obvious their link to PCa. As a result, it may not be clear to PCa patients that hereditary mutations in these genes affect them, as their names only indicate a link to breast and ovarian cancers. To address this misconception, one proposal is to change the name of HBOC syndrome to remove the sex specificity of the name [71], which may reduce confusion about its relevance to men.

CONCLUSION

It is widely accepted that a subset of PCa susceptibility is attributed to inherited predisposition. Because the identification of alterations in PCa predisposition genes may help inform screening strategies for patients and family members, treatment options in the metastatic setting, and clinical trial enrollment, it will become increasingly important to bridge the gap for PCa patients who are underserved with regard to germline testing. Issues to be addressed include a shortage of genetics professionals, disparities in care, medical mistrust, misinformation, and misunderstanding regarding germline testing, costs, and the understudied link between PCa and breast/ovarian cancer.

REFERENCES

1. American Cancer Society. Prostate Cancer. 2020. https://www.cancer.org/cancer/prostate-cancer.html.
2. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. CA Cancer J Clin. 2021;71:7–33.
3. Pritchard CC, Mateo J, Walsh MF, De Sarkar N, Abida W, Beltran H, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med. 2016;375:443–53.
4. Chornokur G, Dalton K, Borysova ME, Kumar NB. Disparities at presentation, diagnosis, treatment, and survival in African American men, affected by prostate cancer. Prostate. 2011;71:985–97.
5. Gilligan T. Social disparities and prostate cancer: mapping the gaps in our knowledge. Cancer Causes Control. 2005;16:45–53.
6. Gross CP, Smith BD, Wolf E, Andersen M. Racial disparities in cancer therapy: did the gap narrow between 1992 and 2002? Cancer. 2008;112:900–8.
7. Richert-Boe KE, Weinmann S, Shapiro JA, Rybicki BA, Enger SM, Van Den Eeden SK, et al. Racial differences in treatment of early-stage prostate cancer. Urology. 2008;71:1172–6.

8. Krimphove MJ, Cole AP, Fletcher SA, Harmouch SS, Berg S, Lipsitz SR, et al. Evaluation of the contribution of demographics, access to health care, treatment, and tumor characteristics to racial differences in survival of advanced prostate cancer. Prostate Cancer Prostatic Dis. 2019;22:125–36.
9. Odedina FT, Akinremi TO, Chinegwundoh F, Roberts R, Yu D, Reams RR, et al. Prostate cancer disparities in Black men of African descent: a comparative literature review of prostate cancer burden among Black men in the United States, Caribbean, United Kingdom, and West Africa. Infect Agent Cancer. 2009;4 Suppl 1:S2.
10. Chinea FM, Patel VN, Kwon D, Lamichhane N, Lopez C, Punnen S, et al. Ethnic heterogeneity and prostate cancer mortality in Hispanic/Latino men: a population-based study. Oncotarget. 2017;8:69709–21.
11. Dobbs RW, Malhotra NR, Abern MR, Moreira DM. Prostate cancer disparities in Hispanics by country of origin: a nationwide population-based analysis. Prostate Cancer Prostatic Dis. 2019;22:159–67.
12. Katz JE, Chinea FM, Patel VN, Balise RR, Venkatramani V, Gonzalgo ML, et al. Disparities in Hispanic/Latino and non-Hispanic Black men with low-risk prostate cancer and eligible for active surveillance: a population-based study. Prostate Cancer Prostatic Dis. 2018;21:533–8.
13. Nicolosi P, Ledet E, Yang S, Michalski S, Freschi B, O'Leary E, et al. Prevalence of germline variants in prostate cancer and implications for current genetic testing guidelines. JAMA Oncol. 2019;5:523–8.
14. Rencsok EM, Bazzi LA, McKay RR, Huang FW, Friedant A, Vinson J, et al. Diversity of enrollment in prostate cancer clinical trials: current status and future directions. Cancer Epidemiol Biomark Prev. 2020;29:1374–80.
15. Kwon DH, Borno HT, Cheng HH, Zhou AY, Small EJ. Ethnic disparities among men with prostate cancer undergoing germline testing. Urol Oncol. 2020;38:80.e1–7.
16. Borno HT, Odisho AY, Gunn CM, Pankowska M, Rider JR. Disparities in precision medicine-examining germline genetic counseling and testing patterns among men with prostate cancer. Urol Oncol. 2021;39:233.e9–14.
17. Dharwadkar P, Greenan G, Stoffel EM, Burstein E, Pirzadeh-Miller S, Lahiri S, et al. Racial and ethnic disparities in germline genetic testing of patients with young-onset colorectal cancer. Clin Gastroenterol Hepatol. 2020;S1542-3565:31721–3.
18. Yip CH, Evans DG, Agarwal G, Buccimazza I, Kwong A, Morant R, et al. Global disparities in breast cancer genetics testing, counselling and management. World J Surg. 2019;43:1264–70.
19. Parikh DA, Dickerson JC, Kurian AW. Health disparities in germline genetic testing for cancer susceptibility. Cur Breast Cancer Rep. 2020;12:51–8.
20. Bureau UC. Table 4. Projected race and Hispanic origin 2017. 2021. https://www.census.gov/data/tables/2017/demo/popproj/2017-summary-tables.html.
21. Berchuck JE, Zhang Z, Silver R, Kwak L, Xie W, Lee GM, et al. Impact of pathogenic germline DNA damage repair alterations on response to intense neoadjuvant androgen deprivation therapy in high-risk localized prostate cancer. Eur Urol. 2021;S0302-2838:00237–2.
22. Shaya JNS, Hatchell KE, Esplin ED, Nussbaum L, Weise N, Madlensky L, et al. Germline alterations among Hispanic men with prostate cancer. J Clin Oncol. 2021;39:10534.
23. Ledet EM, Burgess EF, Sokolova AO, Jaeger EB, Hatton W, Moses M, et al. Comparison of germline mutations in African American and Caucasian men with metastatic prostate cancer. Prostate. 2021;81:433–9.
24. Mahal BA, Alshalalfa M, Kensler KH, Chowdhury-Paulino I, Kantoff P, Mucci LA, et al. Racial differences in genomic profiling of prostate cancer. N Engl J Med. 2020;383:1083–5.
25. Hall MJ, Olopade OI. Disparities in genetic testing: thinking outside the BRCA box. J Clin Oncol. 2006;24:2197–203.
26. Ndugga-Kabuye MK, Issaka RB. Inequities in multi-gene hereditary cancer testing: lower diagnostic yield and higher VUS rate in individuals who identify as Hispanic, African or Asian and Pacific Islander as compared to European. Fam Cancer. 2019;18:465–9.
27. Daly MB, Pal T, Buys SS, Dickson P, Domchek SM, Elkhanany A, et al. Genetic/familial high-risk assessment: breast, ovarian, and pancreatic, version 1.2022, NCCN Clinical Practice Guidelines in Oncology. 2021. https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf.
28. Schaeffer E, Srinivas S, Antonarakis ES, Armstrong AJ, Cheng HH, D'Amico AV, et al. Prostate Cancer, Version 1.2022, NCCN Clinical Practice Guidelines in Oncology. 2021. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.
29. Spratt DE, Chan T, Waldron L, Speers C, Feng FY, Ogunwobi OO, et al. Racial/ethnic disparities in genomic sequencing. JAMA Oncol. 2016;2:1070–4.
30. Na R, Zheng SL, Han M, Yu H, Jiang D, Shah S, et al. Germline mutations in ATM and BRCA1/2 distinguish risk for lethal and indolent prostate cancer and are associated with early age at death. Eur Urol. 2017;71:740–7.
31. Merseburger AS, Waldron N, Ribal MJ, Heidenreich A, Perner S, Fizazi K, et al. Genomic testing in patients with metastatic castration-resistant prostate cancer: a pragmatic guide for clinicians. Eur Urol. 2021;79:519–29.
32. Food and Drug Administration. FDA approves olaparib for HRR gene-mutated metastatic castration-resistant prostate cancer. 2020. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-olaparib-hrr-gene-mutated-metastatic-castration-resistant-prostate-cancer.
33. Food and Drug Administration. FDA grants accelerated approval to rucaparib for BRCA-mutated metastatic castration-resistant prostate cancer. 2020. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-rucaparib-brca-mutated-metastatic-castration-resistant-prostate.
34. Loeb S, Giri VN. Clinical implications of germline testing in newly diagnosed prostate cancer. Eur Urol Oncol. 2021;4:1–9.
35. Antonarakis ES, Piulats JM, Gross-Goupil M, Goh J, Ojamaa K, Hoimes CJ, et al. Pembrolizumab for treatment-refractory metastatic castration-resistant prostate cancer: multicohort, open-label phase II KEYNOTE-199 study. J Clin Oncol. 2020;38:395–405.
36. Sabol RA, Ledet EM, Jaeger E, Hatton W, Moses M, Lankford A, et al. Family history and pathogenic/likely pathogenic germline variants in prostate cancer patients. Prostate. 2021;81:427–32.
37. Berninger T, Nusbaum R, Redlinger-Grosse K, Davis C, Reiser C. A narrative literature review: Growing the workforce through increased fieldwork capacity in genetic counseling training programs. J Genet Couns. 2021;30:574–87.
38. Delikurt T, Williamson GR, Anastasiadou V, Skirton H. A systematic review of factors that act as barriers to patient referral to genetic services. Eur J Hum Genet. 2015;23:739–45.
39. Szymaniak BM, Facchini LA, Giri VN, Antonarakis ES, Beer TM, Carlo MI, et al. Practical considerations and challenges for germline genetic testing in patients with prostate cancer: recommendations from the germline genetics working group of the PCCTC. JCO Oncol Pract. 2020;16:811–9.
40. Villegas C, Haga SB. Access to genetic counselors in the southern United States. J Pers Med. 2019;9:1–33.
41. Shur N, Atabaki SM, Kisling MS, Tabarani A, Williams C, Fraser JL, et al. Rapid deployment of a telemedicine care model for genetics and metabolism during COVID-19. Am J Med Genet A 2021;185:68–72.
42. Rana HQSJ, Petrucelli N, Koeller DR, Pirzadeh-Miller S, Reys B, Kipnis L, et al. A randomized controlled trial of video-education or in-person genetic counseling for men with prostate cancer (ProGen). J Clin Oncol. 2020;38:1507.
43. Nelson A. Unequal treatment: confronting racial and ethnic disparities in health care. J Natl Med Assoc. 2002;94:666–8.
44. Rogers CR, Rovito MJ, Hussein M, Obidike OJ, Pratt R, Alexander M, et al. Attitudes toward genomic testing and prostate cancer research among Black men. Am J Prev Med. 2018;0 5 Suppl 1:S103–11.
45. Shields AE, Burke W, Levy DE. Differential use of available genetic tests among primary care physicians in the United States: results of a national survey. Genet Med. 2008;10:404–14.
46. Zhen JT, Syed J, Nguyen KA, Leapman MS, Agarwal N, Brierley K, et al. Genetic testing for hereditary prostate cancer: current status and limitations. Cancer. 2018;124:3105–17.
47. Hammond WP, Matthews D, Mohottige D, Agyemang A, Corbie-Smith G. Masculinity, medical mistrust, and preventive health services delays among community-dwelling African-American men. J Gen Intern Med. 2010;25:1300–8.
48. LaVeist TA, Isaac LA, Williams KP. Mistrust of health care organizations is associated with underutilization of health services. Health Serv Res. 2009;44:2093–105.
49. Sarver JH, Cydulka RK, Baker DW. Usual source of care and nonurgent emergency department use. Acad Emerg Med. 2002;9:916–23.
50. Allen JD, Kennedy M, Wilson-Glover A, Gilligan TD. African-American men's perceptions about prostate cancer: implications for designing educational interventions. Soc Sci Med. 2007;64:2189–200.
51. American Academy of Medical Colleges. Diversity in medicine: facts and figures 2019. 2019. https://www.aamc.org/data-reports/workforce/interactive-data/figure-18-percentage-all-active-physicians-race/ethnicity-2018.
52. National Society of Genetic Counselors. 2021 Professional status survey: executive summary. 2020. https://www.nsgc.org/Portals/0/Executive%20Summary%202021%20FINAL%2005-03-21.pdf.
53. Alsan MGO, Graziani GC. Does diversity matter for health? Experimental evidence from Oakland. Am Econ Rev. 2019;109:4071–111.
54. Shaw A, Ahmed M. Translating genetics leaflets into languages other than English: lessons from an assessment of Urdu materials. J Genet Couns. 2004;13:321–42.
55. Bouye KE, McCleary KJ, Williams KB. Increasing diversity in the health professions: reflections on student pipeline programs. J Health Sci Humanit. 2016;6:67–79.
56. Halbert CH, Harrison BW. Genetic counseling among minority populations in the era of precision medicine. Am J Med Genet C Semin Med Genet. 2018;178:68–74.
57. Chapman EN, Kaatz A, Carnes M. Physicians and implicit bias: how doctors may unwittingly perpetuate health care disparities. J Gen Intern Med. 2013;28:1504–10.
58. National Institutes of Health NHGRP. The Genetic Information Nondiscrimination Act of 2008. 2021. https://www.genome.gov/27568492/the-genetic-information-nondiscrimination-act-of-2008.

59. Saulsberry K, Terry SF. The need to build trust: a perspective on disparities in genetic testing. Genet Test Mol Biomark. 2013;17:647–8.
60. Cackowski FC, Mahal B, Heath EI, Carthon B. Evolution of disparities in prostate cancer treatment: is this a new normal? Am Soc Clin Oncol Educ Book. 2021;41:1–12.
61. Allford A, Qureshi N, Barwell J, Lewis C, Kai J. What hinders minority ethnic access to cancer genetics services and what may help? Eur J Hum Genet. 2014;22:866–74.
62. Keisler-Starkey KBL Health Insurance Coverage in the United States: 2019 Current Population Reports: US Department of Commerce, US Census Bureau. 2020. https://www.census.gov/content/dam/Census/library/publications/2020/demo/p60-271.pdf.
63. Ward E, Halpern M, Schrag N, Cokkinides V, DeSantis C, Bandi P, et al. Association of insurance with cancer care utilization and outcomes. CA Cancer J Clin. 2008;58:9–31.
64. Yabroff KR, Zhao J, de Moor JS, Sineshaw HM, Freedman AN, Zheng Z, et al. Factors associated with oncologist discussions of the costs of genomic testing and related treatments. J Natl Cancer Inst. 2020;112:498–506.
65. Color Genomics. Products. 2021. https://www.color.com/providers/products.
66. Invitae. Detect Hereditary Prostate Cancer. 2021. https://www.invitae.com/en/detect-hereditary-prostate-cancer/.
67. Promise. 2021. https://www.prostatecancerpromise.org/.
68. Petrucelli N, Daly MB, Pal T. BRCA1- and BRCA2-associated hereditary breast and ovarian cancer. GeneReviews. 1998:1993–2021.
69. Giri VN, Hegarty SE, Hyatt C, O'Leary E, Garcia J, Knudsen KE, et al. Germline genetic testing for inherited prostate cancer in practice: implications for genetic testing, precision therapy, and cascade testing. Prostate. 2019;79:333–9.
70. Armstrong K, Micco E, Carney A, Stopfer J, Putt M. Racial differences in the use of BRCA1/2 testing among women with a family history of breast or ovarian cancer. JAMA. 2005;293:1729–36.
71. Pritchard CC. New name for breast-cancer syndrome could help to save lives. Nature. 2019;571:27–9.
72. Sweeney CJ, Chen YH, Carducci M, Liu G, Jarrard DF, Eisenberger M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med. 2015;373:737–46.
73. James ND, Sydes MR, Clarke NW, Mason MD, Dearnaley DP, Spears MR, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet. 2016;387:1163–77.
74. Fizazi K, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev BY, et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med. 2017;377:352–60.
75. James ND, de Bono JS, Spears MR, Clarke NW, Mason MD, Dearnaley DP, et al. Abiraterone for prostate cancer not previously treated with hormone therapy. N Engl J Med. 2017;377:338–51.
76. Chi KN, Agarwal N, Bjartell A, Chung BH, Pereira de Santana Gomes AJ, Given R, et al. Apalutamide for metastatic, castration-sensitive prostate cancer. N Engl J Med. 2019;381:13–24.
77. Armstrong AJ, Szmulewitz RZ, Petrylak DP, Holzbeierlein J, Villers A, Azad A. at al. ARCHES: a randomized, phase III study of androgen deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer. J Clin Oncol. 2019 ;37:2974–86.
78. Davis ID, Martin AJ, Stockler MR, Begbie S, Chi KN, Chowdhury S, et al. Enzalutamide with standard first-line therapy in metastatic prostate cancer. N Engl J Med. 2019;381:121–31.
79. Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med. 2004;351:1502–12.
80. de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet. 2010;376:1147–54.
81. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med. 2010;363:411–22.
82. Parker C, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, Fosså SD, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med. 2013;369:213–23.
83. de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med. 2011;364:1995–2005.
84. Ryan CJ, Smith MR, de Bono JS, Molina A, Logothetis CJ, de Souza P, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med. 2013;368:138–48.
85. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012;367:1187–97.
86. Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med. 2014;371:424–33.
87. Smith MR, Saad F, Chowdhury S, Oudard S, Hadaschik BA, Graff JN, et al. Apalutamide treatment and metastasis-free survival in prostate cancer. N Engl J Med. 2018;378:1408–18.
88. Hussain M, Fizazi K, Saad F, Rathenborg P, Shore N, Ferreira U, et al. Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. N Engl J Med. 2018;378:2465–74.
89. Fizazi K, Shore N, Tammela TL, Ulys A, Vjaters E, Polyakov S, et al. Darolutamide in nonmetastatic, castration-resistant prostate cancer. N Engl J Med. 2019;380:1235–46.
90. Giri VN, Knudsen KE, Kelly WK, Cheng HH, Cooney KA, Cookson MS, et al. Implementation of germline testing for prostate cancer: Philadelphia Prostate Cancer Consensus Conference 2019. J Clin Oncol. 2020;38:2798–811.
91. Lowrance WT, Breau RH, Chou R, Chapin BF, Crispino T, Dreicer R, et al. Advanced prostate cancer: AUA/ASTRO/SUO Guideline PART I. J Urol. 2021;205:14–21.
92. Lowrance WT, Breau RH, Chou R, Chapin BF, Crispino T, Dreicer R, et al. Advanced prostate cancer: AUA/ASTRO/SUO Guideline PART II. J Urol. 2021;205:22–9.
93. Sanda MG, Chen RC, Crispino T, Freedland S, Greene K, Klotz LH, et al. Clinically localized prostate cancer: AUA/ASTRO/SUO Guideline: American Urological Association. 2017. https://www.auanet.org/guidelines/guidelines/prostate-cancer-clinically-localized-guideline#x6914.

ACKNOWLEDGEMENTS

PNW SPORE CA097186; Congressional Designated Medical Research Program (CDMRP) award W81XWH-17-2-0043; P30 CA015704; Prostate Cancer Foundation

AUTHOR CONTRIBUTIONS

Concept and design: RRM. Acquisition, analysis or interpretation of data: NW, JS. Drafting of paper: NW, RRM. Critical revisions of paper for important intellectual content: NW, JS, JJD, HHC, LM, and RRM. Approval of final paper: NW, JS, JJD, HHC, LM, and RRM. Supervision: RRM.

COMPETING INTERESTS

HHC received research funding to her institution from Astellas, Clovis Oncology, Color Foundation, Janssen, Medivation, Phosplatin, and Sanofi; is a consultant for AstraZeneca. RRM received research funding from Bayer, Pfizer, Tempus; serves on Advisory Board for AstraZeneca, Bayer, Bristol Myers Squibb, Calithera, Exelixis, Janssen, Merck, Novartis, Pfizer, Sanofi, Tempus; is a consultant for Dendreon, Myovant, Vividion; serves on the molecular tumor board at Caris. The remaining authors declare no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Rana R. McKay.

Circulating and Intratumoral Adrenal Androgens Correlate with Response to Abiraterone in Men with Castration-Resistant Prostate Cancer

Elahe A. Mostaghel[1,2,3], Brett T. Marck[1], Orpheus Kolokythas[4], Felix Chew[4], Evan Y. Yu[2,3], Michael T. Schweizer[2], Heather H. Cheng[2], Phillip W. Kantoff[5], Steven P. Balk[6], Mary-Ellen Taplin[7], Nima Sharifi[8,9,10], Alvin M. Matsumoto[1,11], Peter S. Nelson[3], and R. Bruce Montgomery[2,3,12]

ABSTRACT

Purpose: In metastatic castration-resistant prostate cancer (mCRPC) low serum androgens prior to starting abiraterone acetate (AA) is associated with more rapid progression. We evaluated the effect of AA on androgens in castration-resistant prostate cancer (CRPC) metastases and associations of intratumoral androgens with response.

Experimental Design: We performed a phase II study of AA plus prednisone in mCRPC. The primary outcome was tissue testosterone at 4 weeks. Exploratory outcomes were association of steroid levels and genomic alterations with response, and escalating AA to 2,000 mg at progression.

Results: Twenty-nine of 30 men were evaluable. Testosterone in metastatic biopsies became undetectable at 4 weeks ($P < 0.001$). Serum and tissue dehydroepiandrosterone sulfate (DHEAS) remained detectable in many patients and was not increased at progression. Serum and tissue DHEAS in the lowest quartile (pretreatment), serum DHEAS in the lowest quartile (4 weeks), and undetectable tissue DHEAS (on-therapy) associated with rapid progression (20 vs. 48 weeks, $P = 0.0018$; 20 vs. 52 weeks, $P = 0.0003$; 14 vs. 40 weeks, $P = 0.0001$; 20 vs. 56 weeks, $P = 0.02$, respectively). One of 16 men escalating to 2,000 mg had a 30% PSA decline; 13 developed radiographic progression by 12 weeks. Among patients with high serum DHEAS at baseline, wild-type (WT) PTEN status associated with longer response (61 vs. 33 weeks, $P = 0.02$).

Conclusions: Low-circulating adrenal androgen levels are strongly associated with an androgen-poor tumor microenvironment and with poor response to AA. Patients with CRPC with higher serum DHEAS levels may benefit from dual androgen receptor (AR)-pathway inhibition, while those in the lowest quartile may require combinations with non–AR-directed therapy.

[1]Geriatric Research, Education and Clinical Center (GRECC), U.S. Department of Veterans Affairs Puget Sound Health Care System, Seattle, Washington. [2]Division of Medical Oncology, Department of Medicine, University of Washington, Seattle, Washington. [3]Fred Hutchinson Cancer Research Center, Seattle, Washington. [4]Department of Radiology, University of Washington, Seattle, Washington. [5]Memorial Sloan Kettering Cancer Center, New York, New York. [6]Beth Israel Deaconess Medical Center, Boston, Massachusetts. [7]Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts. [8]Genitourinary Malignancies Research Center, Lerner Research Institute, Cleveland Clinic, Cleveland, Ohio. [9]Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, Ohio. [10]Taussig Cancer Institute, Cleveland Clinic, Cleveland, Ohio. [11]Division of Gerontology & Geriatric Medicine, Department of Medicine, University of Washington, Seattle, Washington. [12]Division of Hematology and Oncology, VA Puget Sound Health Care System, Seattle, Washington.

Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

ClinicalTrial registration: ClinicalTrials.gov NCT01503229.

Corresponding Authors: Elahe A. Mostaghel, Geriatric Research, Education and Clinical Center (GRECC), U.S. Department of Veterans Affairs Puget Sound Health Care System, 1600 South Columbian Way, Seattle, WA 98108. E-mail: emostagh@fredhutch.org; and R.B. Montgomery, Division of Medical Oncology, Department of Medicine, RR-512, Health Sciences Building, University of Washington, Box 356420, 1959 NE Pacific Street, Seattle, WA 98195-6420. E-mail: rbmontgo@uw.edu

Clin Cancer Res 2021;27:6001–11

doi: 10.1158/1078-0432.CCR-21-1819

Introduction

While initially effective, treatment of prostate cancer with androgen deprivation therapy (ADT) is uniformly characterized by progression to castration-resistant prostate cancer (CRPC). Despite castrate-serum testosterone (T) levels, levels of T and DHT in CRPC metastases and patient-derived xenografts (PDX) are sufficient for androgen receptor (AR) activation (1, 2). Residual androgens in CRPC tumors may reflect *de novo* androgen synthesis or intratumoral uptake and conversion of adrenally derived steroid precursors to T and DHT (3, 4). In particular, serum levels of dehydroepiandrosterone sulfate (DHEAS), the primary circulating form of the adrenal androgen DHEA, are extremely high and are not suppressed by ADT (5, 6).

CYP17A, expressed in the adrenal gland, testes, and ovary, catalyzes sequential reactions converting pregnenolone and progesterone to the adrenal androgens DHEA and androstenedione (AED). The role of adrenal androgens in promoting CRPC is supported by the efficacy of the CYP17A inhibitor abiraterone acetate (AA) in decreasing circulating adrenal androgens and improving overall survival (OS) in CRPC (7–10). The proposed mechanism is suppression of androgen levels in tumor tissue as a result of suppressing testicular, adrenal, and tumoral CYP17A activity. This regimen markedly decreases prostate androgens below that achieved by standard ADT in the neoadjuvant setting (5) and studies using CRPC xenografts similarly demonstrate suppression of tissue androgens below castration alone (11). However, the efficacy of AA and prednisone in reducing intratumoral androgens in CRPC metastases has not been reported. Moreover, lower serum androgen levels prior to starting this regimen have been associated with worse outcomes in patients with CRPC (12, 13). Whether a similar association exists with intratumoral androgen levels prior to

Translational Relevance

In men with metastatic castration-resistant prostate cancer (CRPC), low-circulating adrenal androgens levels are strongly associated with an androgen-poor tumor microenvironment, with lower androgen levels while on-therapy, and with poor response to abiraterone acetate (AA) plus prednisone. While response to AA is clearly linked with its ability to suppress circulating and intratumor androgen levels, the paradoxical association of lower adrenal androgen levels while on-therapy with more rapid radiographic progression suggests an intrinsic resistance to androgen receptor (AR)-pathway therapy related to tumor outgrowth in a low androgen microenvironment. These data suggest that clinical benefit from dual-AR pathway inhibition is likely to be observed in patients with higher serum adrenal androgen levels, but will be limited in those with low/undetectable levels in whom treatment combinations with non–AR-directed therapy are likely to be required. Assessment of baseline and on-treatment androgen levels can inform the stratification and interpretation of trials evaluating the efficacy of AR pathway–directed therapy.

starting therapy, or with on-treatment androgen levels in serum or tissue is unknown.

We carried out a phase II study to evaluate the efficacy of AA plus prednisone in reducing androgen levels in CRPC metastases. The primary outcome was tissue T levels at 4 weeks. Exploratory outcomes were the association of steroid levels and genomic alterations with response, and the impact of escalating AA to 2,000 mg at progression.

Materials and Methods

Study design and patient population

This was an investigator-initiated open-label single-center three-arm study of AA (1,000 mg daily) and prednisone (5 mg twice daily) followed by escalation of AA to 2,000 mg daily at disease progression in men with metastatic castration-resistant prostate cancer (mCRPC). Eligible patients had metastatic prostate cancer resistant to ADT comprised of medical or surgical castration ± standard antiandrogen (bicalutamide, flutamide, or nilutamide) and were not previously treated with AA or enzalutamide. Prior ketoconazole and docetaxel were allowed.

Study procedures and treatment

Patients underwent pretreatment biopsy of a bone, node, or soft-tissue metastasis and were then alternately enrolled in cohorts undergoing repeat biopsy at 4 weeks (cohort 1) or 12 weeks (cohort 2) until 10 patients were enrolled in each cohort (Study Schema provided in Supplementary Fig. S1). Patients with radiographic or clinical progression prior to planned biopsy were reassigned to cohort 3 (biopsy at progression) and another patient placed in cohort 1 or 2. After cohorts 1 and 2 were filled, patients were sequentially assigned to cohort 3 with biopsy at progression, until a total of 10 patients were enrolled in cohort 3 (of these, 2 had been reassigned from cohort 1 or 2 for clinical progression at 4 and 8 weeks). Patients remained on ADT and received AA 1,000 mg orally daily with prednisone 5 mg orally twice daily until development of radiographic or clinical progression. CT of the chest, abdomen, and pelvis, and bone scan were obtained before enrollment and every 12 weeks while on study treatment. Radiographic progression was determined based on Prostate Cancer Working Group 2 (PCWG2) criteria. Serum for PSA was drawn monthly. At radiographic progression asymptomatic patients were offered dose escalation of AA to 2,000 mg daily. Therapy with standard or dose-escalated AA was continued until radiographic or clinical progression or for a maximum of 2 years (104 weeks).

Steroid and abiraterone measurements

Methods for determination of steroids and abiraterone in serum and prostate tissue by mass spectrometry were as previously reported (14). Similar methods were used for detection of the abiraterone metabolites D4-abiraterone, and 3-keto-5α-abiraterone. Additional information on assay methodology and limits of detection and quantitation is provided in Supplementary Fig. S2. For purposes of calculation, analyte values below the lower limit of detection were set at the lower limit of quantitation specific for that analyte.

Genomic analysis

Genomic DNA was prepared from clinical samples (buffy coat, mCRPC tumor tissue) using DNeasy Blood and Tissue Kit (QIAGEN). Next-generation sequencing (NGS) was performed on CRPC tissue biopsies using the clinically validated UW-OncoPlex platform (15). We determined *HSD3B1* genotype in DNA extracted from buffy coat using a melting assay with an unlabeled, locked, nucleic acid oligonucleotide probe in an asymmetric PCR as previously described (16).

Statistical analysis

A sample size of 6 patients per arm provided 94% power to detect the anticipated 0.660 pg/mg difference in tissue T levels relative to baseline, based on a 2-sided paired *t* test with alpha 5%. Ten patients per cohort were enrolled to account for potentially unproductive biopsies. Demographic and clinical characteristics were summarized using descriptive statistics. Comparisons of continuous variables among groups were assessed using the nonparametric Wilcoxon rank–sum test (Mann–Whitney test). Comparison of continuous variables between baseline and subsequent timepoints were assessed using the Wilcoxon matched-pairs test. Progression-free survival (PFS) was estimated using Kaplan–Meier methods and compared using the Gehan–Wilcoxan test. The statistical significance was set at $P < 0.05$. Due to the small sample size, all findings were considered hypothesis generating and no multiple-testing adjustments were performed. All statistical analyses were done using GraphPad Prism (version 8.3.0).

Study approval

All procedures were carried out in accordance with the U.S. Common Rule and approved by the institutional review board of the University of Washington. All subjects signed written informed consent. The trial was registered with the clinicaltrials.gov identifier NCT01503229.

Results

Patient characteristics

Thirty patients enrolled and 29 were evaluable for analysis (**Fig. 1**). Baseline characteristics are shown in **Table 1**. Median age was 71 years (range 44–83 years). The median PSA was 78 ng/mL (range 2–908). In the 18 patients with soft-tissue ± bone disease, the biopsy site was equally divided between bone and lymph node based solely on tumor location most accessible to biopsy. Eleven patients had received previous definitive therapy for localized disease while 19 were metastatic at diagnosis. Eleven patients had received one or more treatments beyond bicalutamide for CRPC.

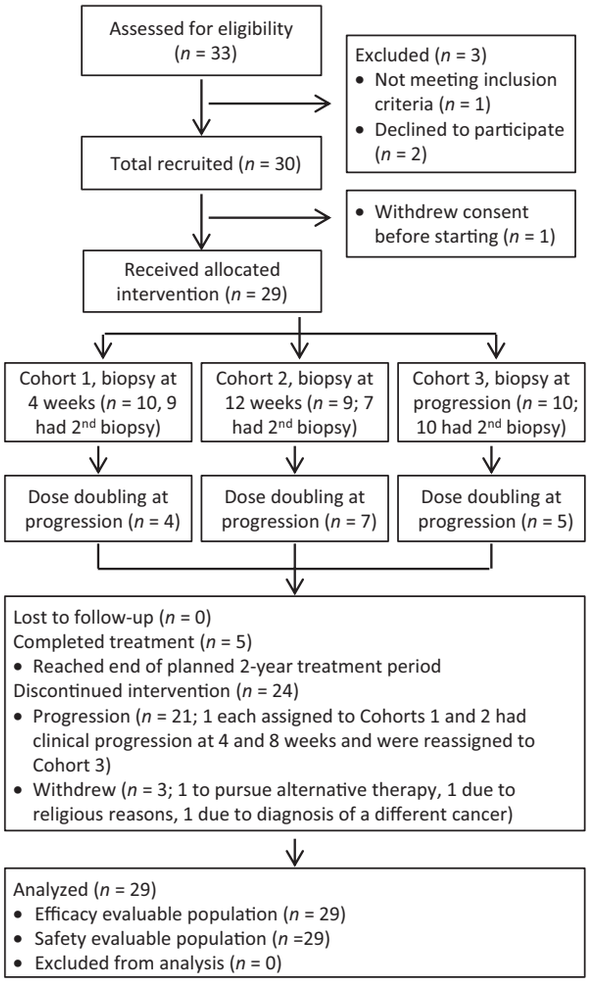


Figure 1.

Flow diagram of patient recruitment, enrollment, and participation. Diagram depicts participant flow through the study process from patient screening to data analysis.

Clinical response to standard and dose-escalated AA and prednisone

The median time-to–radiographic/clinical progression in the entire cohort was 36 weeks (range 4–104; **Fig. 2A**). Twenty of 29 (69%) achieved a PSA decline of ≥30% (PSA30) after 12 weeks of standard-dose AA plus prednisone (**Fig. 2B**), with 22 (75%) eventually doing so. The median time-to-progression was longer in those achieving PSA30 decline at 12 weeks (40 vs. 34 weeks; $P = 0.05$; with a similar but nonsignificant trend in those achieving a PSA50 decline; Supplementary Fig. S3A and S3B; ref. 17). Notably, 4 of the 9 patients without PSA30 at 12 weeks had responses lasting 36, 40, 41, and 104 months, underscoring the importance of radiographic progression versus PSA decline as a primary endpoint. Three patients withdrew while responding to therapy (1 each to pursue alternative therapy, for religious reasons, and due to diagnosis of an unrelated malignancy) and were censored at the time of study withdrawal (at 28, 24, and 20 months). Three patients did not progress on standard-dose therapy by the end of the 2-year treatment period and were censored at 104 months.

Table 1. Baseline clinical characteristics at time of study enrollment.

Patients, *n*	29
Median age (range), years	71 (44–83)
Median PSA (range), ng/mL	78 (2–908)
Extent of disease	
Bone only	10 (33%)
Bone and LAD	15 (50%)
Bone and LAD/visceral disease	3 (10%)
LAD only	2 (7%)
Median tumor fraction in prestudy biopsy	55% (4–88%)
Previous therapies, *n*	
Radical prostatectomy	5
Definitive radiotherapy	6
Neither (metastatic at diagnosis)	19
Systemic therapy	
Combined androgen blockade	8
Bicalutamide	9
Nilutamide/flutamide	3
High-dose ketoconazole	5
Diethylstilbestrol	2
Sipuleucel-T	4
Docetaxel	4 (1 CSPC)
Lines of therapy for CRPC	
0	7
1	14
2	3
3–4	5

Abbreviations: CSPC, castration-sensitive prostate cancer; LAD, lymphadenopathy.

At radiographic progression, 16 of 29 patients underwent dose escalation of AA to 2,000 mg per day (with continuation of prednisone). There was no decrease in the median PSA (Supplementary Fig. S3C), with only 1 patient achieving a PSA30 decline (**Fig. 2C**). Thirteen patients had clinical or radiographic progression and discontinued therapy by week 12 after dose escalation. Two patients remained on dose-escalated therapy for 56 weeks and 36 weeks, respectively, prior to second radiographic progression, while 1 patient remained on dose-escalated therapy for 20 weeks at which time he reached the end of the 2-year treatment period and was censored at 104 months. No consistent findings with regards to PSA, steroid, or abiraterone levels, or tumor genomic alterations were observed in these 3 patients.

Steroid and abiraterone levels during standard and dose-escalated AA therapy

Steroid levels in serum and tissue prior to and during AA and prednisone therapy are summarized in Supplementary Tables S1 and S2. Serum levels showed a significant increase in steroids upstream of CYP17A (pregnenolone) and decreases in downstream steroids (DHEAS, DHEA, AED, T, and DHT) at all timepoints (**Fig. 2D**; see steroid metabolism schema, Supplementary Fig. S4), consistent with prior observations in serum and urine (7). While median levels of DHEAS and DHEA decreased by over two orders of magnitude in response to therapy in all patients, there appeared to be two modes of response. In one, levels became undetectable by week 4 and remained undetectable, while in the other subset, levels were still detectable at week 4 and remained detectable at all time points of treatment. AED, T, and DHT in serum were largely undetectable at all time points after starting therapy. Serum steroids were not increased at progression compared with earlier time points.

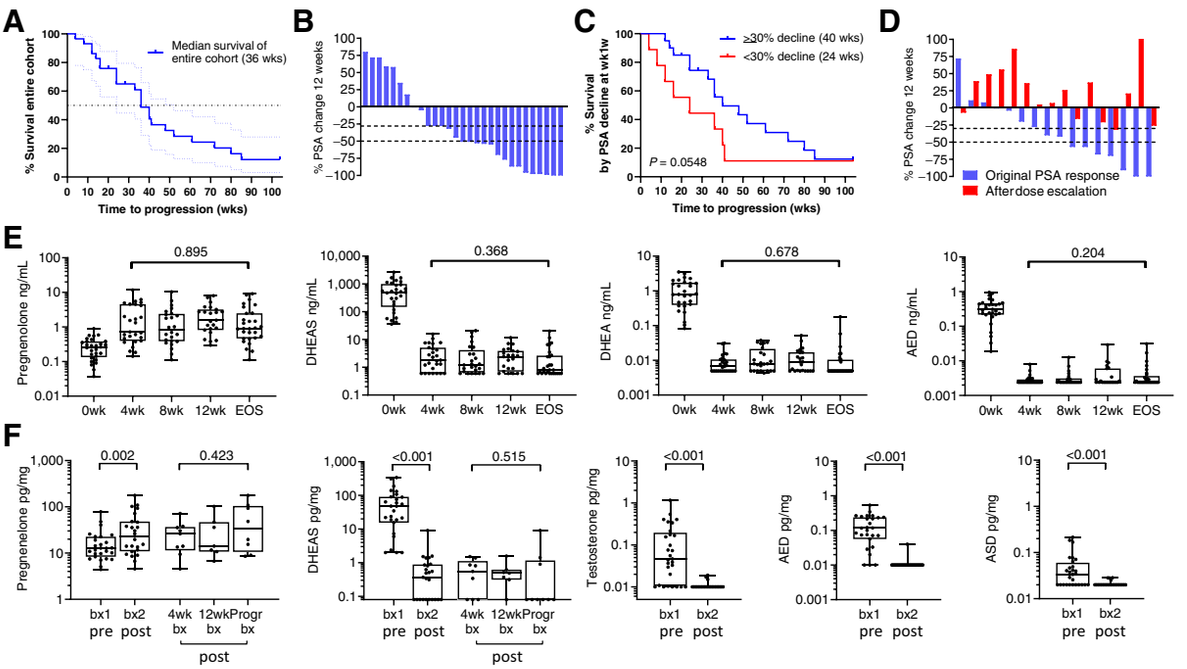


Figure 2.

Clinical response and steroid levels in serum and metastatic tissue on AA plus prednisone. **A,** Kaplan–Meier plot of time to radiographic progression on standard dose AA. **B,** Waterfall plot showing percent change in PSA at 12 weeks. **C,** Kaplan–Meier plot of time to radiographic progression comparing patients with or without a 30% PSA decline at 12 weeks. **D,** Waterfall plot comparing the original change in PSA (blue bars) to the percent change in PSA after dose escalation of AA to 2,000 mg per day (red bars). **E,** Change in serum steroid levels after standard dose AA plus prednisone at baseline (0 weeks); at 4, 8 and 12 weeks (4wk, 8wk, 12wk); and at end of study (EOS) at the time of radiographic progression. **F,** Change in steroid levels in metastatic tissue (tx) biopsies prior to therapy (biopsy 1, bx1) and while on therapy (biopsy 2, bx2). Biopsy 2 was taken at either 4 weeks (4wk bx), 12 weeks (12wk bx), or at progression (Progr bx). *P* values for the indicated comparison calculated via the Wilcoxon matched-pairs test. Data are shown as box and whisker plots, where horizontal lines indicate median values, white boxes denote the 75th (upper margin) and 25th percentiles (lower margin), and upper and lower bars indicate the minimum and maximum values, respectively. AED, androstenedione; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate.

In tissue as in serum, steroids upstream of CYP17A (pregnenolone) were increased in the on-treatment tissue biopsies, while downstream steroids [DHEAS, AED, T, androsterone (ASD)] were significantly decreased (**Fig. 2E**). Levels of AED, T, and ASD in tissue fell below the limit of detection by week 4 and remained essentially undetectable. DHEAS in tissue remained detectable in the majority of biopsies obtained at 4 and 12 weeks (6 of 9 and 6 of 7, respectively), but was undetectable in 6 of 9 samples at progression. DHT levels were below the limit of detection in 24 of 29 tissue samples at baseline and undetectable in all tissues after therapy. These observations suggest that an increase in tissue levels of androgens is not responsible for resistance to AA and prednisone and explains the lack of response to AA dose escalation.

AA is a prodrug that rapidly dissociates to abiraterone once ingested, therefore, all serum and tissue measurements are of abiraterone, not AA (summarized in Supplementary Table S3). Abiraterone is converted by 3βHSD1 to D4-abiraterone, and then by SRD5A to 3-keto-5α-abiraterone, metabolites with AR antagonist and AR-agonist activity, respectively (18). Levels of abiraterone metabolites in serum and tissue were similar at all time points and were not decreased at progression compared with earlier time points (Supplementary Fig. S5A and S5B). These observations suggest that resistance to AA is not associated with an increase in serum steroid levels or decrease in serum or tissue drug levels at the time of progression.

Dose escalation of AA from 1,000 mg to 2,000 mg resulted in the expected pharmacokinetic changes with a nonsignificant increase in the median level of abiraterone (22.4 to 78.2 ng/mL), and a significant increase in D4-abiraterone (1.48 to 4.0; $P = 0.012$) and 3-keto-5α-abiraterone (10.6 to 14.3 ng/mL; $P = 0.005$) at 4 weeks (Supplementary Fig. S5C). Accordingly, serum levels of DHEAS and DHEA decreased in 9 of 16 patients, and AED levels remained or became undetectable in 15 of 16 (Supplementary Fig. S5D), although the overall decrease in median levels was nonsignificant for DHEAS and DHEA, and of borderline significance for AED ($P = 0.21$, 0.36, and 0.06, respectively). These observations suggest that the lack of clinical response to AA dose escalation is not accounted for by a failure of pharmacokinetic or pharmacodynamic responses in serum. Moreover, in the 3 patients that experienced prolonged responses, serum abiraterone and androgen levels after dose escalation were variably altered (decreased in 2 and increased in 1), although changes in tissue levels before and after dose escalation were not assayed.

Correlation of steroid levels in serum and metastatic tissue before and after therapy with AA and prednisone

Serum levels of DHEAS, DHEA, AED, ASD, T, and DHT, were highly correlated with each other and with levels of DHEAS, AED, and ASD in pretreatment biopsies (**Fig. 3A**). Tissue levels of DHEAS and AED, DHEAS and ASD, and AED and ASD correlated with each other ($r = 0.51$, 0.56, and 0.46, respectively; $P < 0.05$ for all), while tissue T levels were not significantly correlated with steroid levels in either serum or tissue. After starting AA plus prednisone, levels of DHEAS,

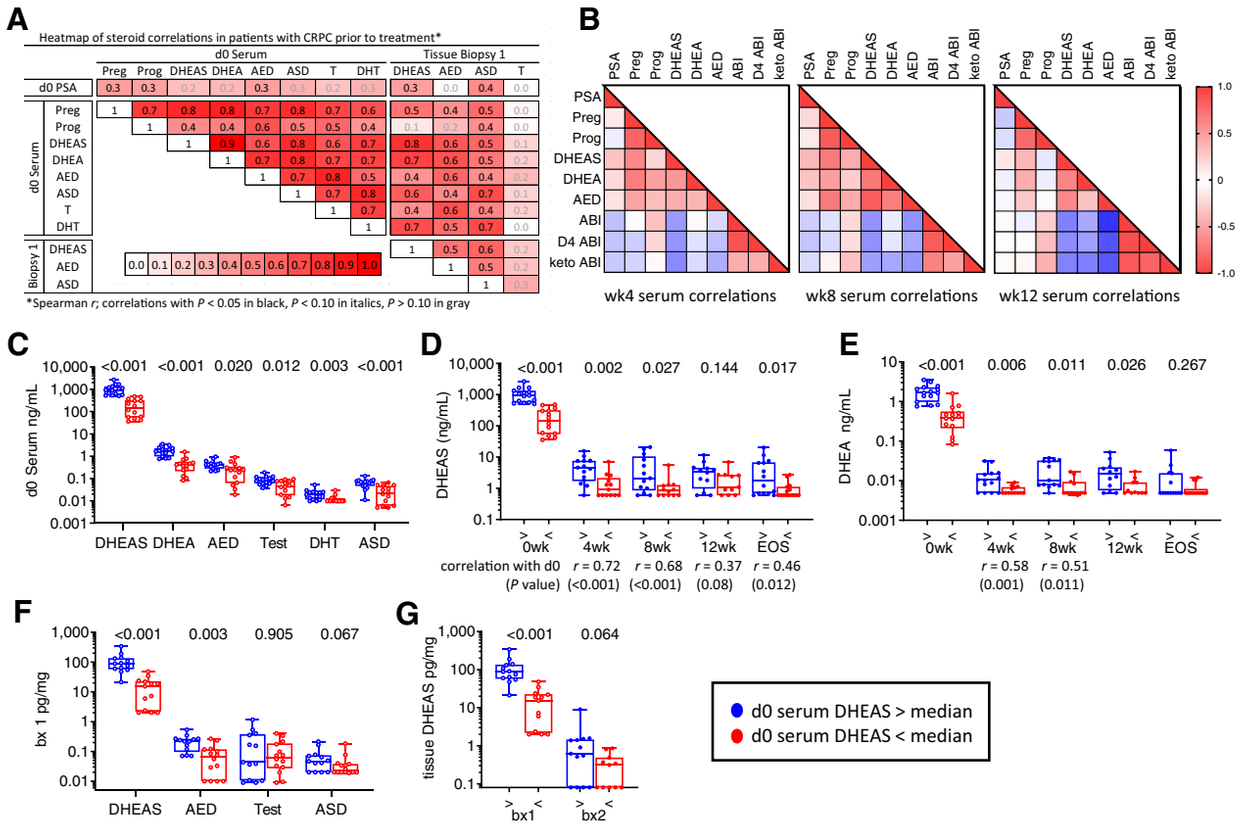


Figure 3.

Correlation of steroid levels in serum and metastatic tissue before and after treatment with AA plus prednisone. **A,** Heatmap of steroid correlations in pretreatment serum (day 0) and metastatic tissue biopsies (Biopsy 1). The Spearman *r* value for each correlation is shown in the box. Correlations with $P < 0.05$ in black, $P < 0.10$ in italics, $P > 0.10$ in gray. **B,** Heatmap of Spearman correlations for steroids in serum at week 4 (wk4), week 8 (wk8), and week 12 (wk12). **C,** Comparison of baseline serum steroid levels stratified by serum DHEAS levels above (blue) versus below (red) the median at baseline (d0). **D** and **E**, Comparison of DHEAS levels (**D**) and DHEA levels (**E**) in serum stratified by baseline serum DHEAS levels at baseline (0 weeks); at 4, 8, and 12 weeks; and at EOS. Significant Spearmen correlations between on-treatment and baseline values at each time point is indicated below the timepoint. **F,** Comparison of steroid levels in pretreatment tissue biopsies (bx 1) stratified by serum DHEAS levels above (blue) vs. below (red) the median at baseline. **G,** Comparison of tissue (tx) DHEAS levels stratified by baseline serum DHEAS levels in pretreatment and on-treatment tissue biopsies (bx1 and bx2). *P* values for the indicated comparison calculated via nonparametric Mann–Whitney *t* tests. ABI, abiraterone; D4 ABI, D4-abiraterone; Keto ABI, 3-keto-5α-abiraterone; Preg, pregnenolone; Prog, progesterone; Test, testosterone.

DHEA, and AED remained significantly correlated with each other and showed the expected inverse correlations with abiraterone and its metabolites (**Fig. 3B**), while progesterone showed the expected positive correlation with abiraterone and its metabolites. These treatment-related correlations were present by 4 weeks and became notably more pronounced at 8 and 12 weeks. Abiraterone and metabolite levels were strongly correlated with each other in serum and tissue at all time points (Supplementary Fig. S6A).

These baseline and on-treatment steroid correlations are further illustrated by the observation that subjects with baseline serum DHEAS levels above versus below the median also had higher baseline levels of DHEA, AED, T, DHT, and ASD (**Fig. 3C**) and maintained significantly higher serum levels of DHEAS (**Fig. 3D**) and DHEA (**Fig. 3E**) at all time points [including, for DHEAS, at the end-of-study (EOS) measurement taken at progression]. Moreover, strong correlations between baseline and on-treatment serum levels were observed at all time points for DHEAS (**Fig. 3D**), and at 4 and 8 weeks for DHEA (**Fig. 3E**). Likewise, subjects with baseline serum DHEAS above versus below the median had higher tissue levels of DHEAS, AED, and ASD at baseline (**Fig. 3F**), as well as higher DHEAS in on-treatment tissue biopsies (**Fig. 3G**). These observations demonstrate that serum DHEAS levels prior to AA therapy can identify patients with CRPC with concomitantly higher levels of all androgens in serum and tissue, and that this subset of patients with high baseline androgen levels maintains persistently higher serum and tissue DHEAS levels after treatment with AA and prednisone.

Association of steroid and abiraterone levels with PSA decline and PFS

Compared with patients who achieved a PSA30 decline at 12 weeks, those with less than a PSA30 decline had numerically lower pretreatment levels of serum and tissue androgens (**Fig. 4A**). These differences were strongest for T ($P = 0.055$) and DHT ($P = 0.069$) in serum, and for AED ($P = 0.063$), T ($P = 0.034$), and ASD ($P = 0.088$) in tissue. Accordingly, the rate of achieving a PSA30 decline at 12 weeks was 37% (3/8) in patients in the lowest quartile of serum DHEAS, but 81% (17/21) in patients in the top 3 quartiles (**Fig. 4C**; PSA levels at baseline were not associated

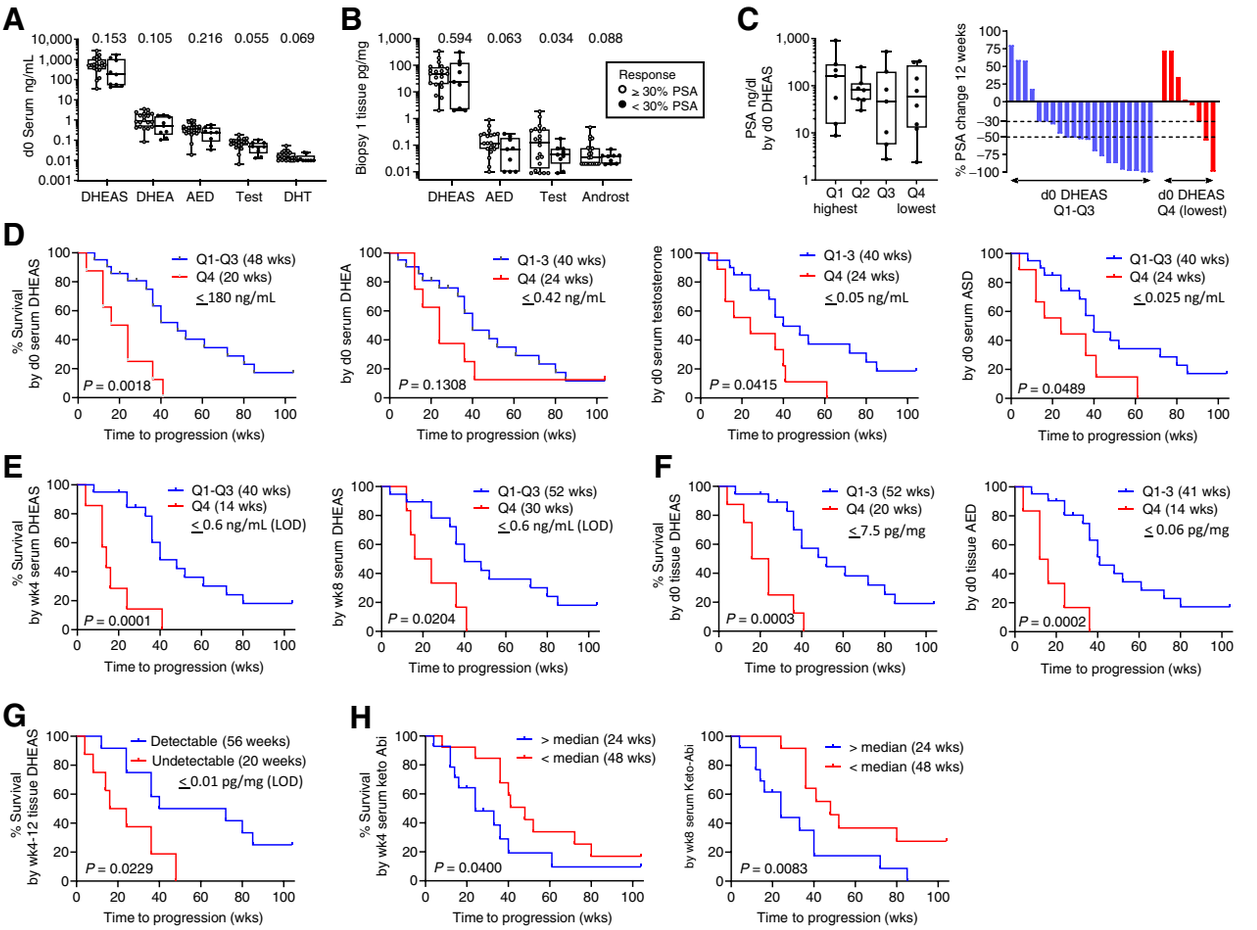


Figure 4.

Association of steroid and abiraterone levels with PSA decline and radiographic progression on AA plus prednisone. **A** and **B,** Comparison of steroid levels in serum (**A**) and metastatic tissue biopsies (**B**), based on achieving a 30% PSA decline at 12 weeks. **C,** Distribution of pretreatment PSA levels and waterfall plot showing percent change in PSA at 12 weeks by quartile (Q1-Q4) of pretreatment serum DHEAS levels. *P* values for the indicated comparison calculated via nonparametric Wilcoxon rank–sum test (Mann–Whitney test). **D,** Radiographic PFS (rPFS) as a function of baseline serum androgen levels comparing subjects in the lowest vs. highest 3 quartiles (Q4 vs. Q1–3). **E,** rPFS as a function of on-treatment serum DHEAS levels at week 4 (wk4) and week 8 (wk8) comparing subjects in the lowest vs. highest 3 quartiles (Q4 vs. Q1–3). **F,** rPFS as a function of pretreatment tissue DHEAS and AED levels comparing subjects in the lowest vs. highest 3 quartiles (Q4 vs. Q1–3). In each case, the cut-off value reflects the highest number of the bottom one-fourth of the values. The quartiles were separately assessed in the pre- and on-treatment populations. **G,** rPFS comparing subjects with detectable vs. undetectable levels of DHEAS in tissue biopsies taken at 4 and 12 weeks of therapy. **H,** rPFS as a function of serum 3-keto-5α-abiraterone levels (keto-Abi) at wk4 and wk8 comparing subjects above vs. below the median. PFS was estimated using Kaplan–Meier methods and compared using the Gehan–Wilcoxan test. Androst, androsterone; Q, quartile.

with serum DHEAS levels). These observations suggest that being in the lowest quartile of serum androgens prior to starting AA therapy is associated with a decreased incidence of PSA30 decline at 12 weeks.

Consistent with these observations, serum steroid levels in the lowest quartile prior to therapy were associated with more rapid progression. This was highly significant for DHEAS (20 vs. 48 weeks, $P = 0.0018$) with less significant trends noted for DHEA, T, and ASD ($P = 0.13$, 0.041, and 0.049 respectively; **Fig. 4D**). Notably, on-treatment levels of DHEAS in the lowest quartile remained associated with more rapid progression (14 vs. 40 weeks, $P = 0.0001$ at 4 weeks; 20 vs. 40 weeks, $P = 0.02$ at 8 weeks; **Fig. 4E**). Low adrenal androgens in pretreatment tissue biopsies were even more strongly associated with worse outcomes (20 vs. 52 weeks, $P = 0.0003$ for DHEAS; 14 vs. 41 weeks, $P = 0.0002$ for AED; **Fig. 4F**). Likewise, undetectable vs. detectable DHEAS levels in biopsies taken at 4 and 12 weeks were associated with shorter time-to-progression (20 vs. 56 weeks, $P = 0.023$; **Fig. 4G**). These observations demonstrate that the association of lower serum adrenal androgen levels with more rapid progression on AA plus prednisone holds true for lower adrenal-androgen levels in pretreatment metastasis biopsies, and for lower on-treatment levels of DHEAS in serum and tissue.

Levels of abiraterone and D4-abiraterone in serum were not associated with differences in time-to-progression, nor were levels of abiraterone and its metabolites in tissue (Supplementary Fig. S6B and S6C). However, serum levels of 3-keto-5α-abiraterone above the median at week 4 and 8 were associated with more rapid progression (24 vs. 48 weeks, $P = 0.04$, and 24 vs. 48 weeks, $P = 0.008$, respectively; **Fig. 4H**), consistent with the ability of this metabolite to act as an AR agonist.

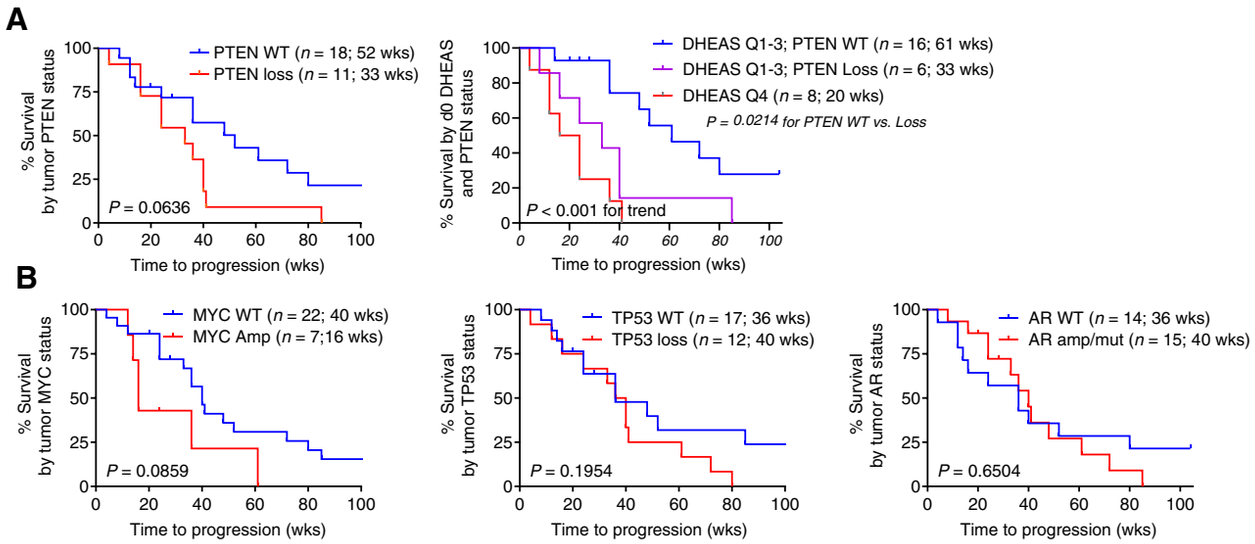


Figure 5.

Association of *PTEN* status with radiographic progression on AA plus prednisone. **A,** rPFS as a function of *PTEN* status alone or as a function of baseline serum DHEAS levels stratified by *PTEN* status, comparing subjects in the lowest vs highest three quartiles (Q4 vs Q1–3). **B,** rPFS as a function of *MYC, TP53*, or *AR* status.

Association of genomic alterations with radiographic PFS on AA and prednisone

All patients had pretreatment tumor biopsy tissue that was adequate for sequencing. The frequency and distribution of pathogenic alterations were consistent with mCRPC (Supplementary Table S4). Wild-type (WT) *PTEN* was weakly associated with longer time-to-progression (52 vs. 33 weeks, $P = 0.06$; **Fig. 5A**). Patients in the lowest quartile of serum DHEAS (3 *PTEN* WT, and 5 *PTEN* loss) were previously shown to have a poor response to AA (**Fig. 4D**) and this was not influenced by *PTEN* status. However, in the top 3 quartiles of serum DHEAS (with median survival 48 weeks; **Fig. 4D**), WT *PTEN* versus *PTEN* loss distinguished patients with a significantly more prolonged versus intermediate response (61 vs. 33 weeks; $P = 0.02$) versus those in the lowest quartile of DHEAS (20 weeks; $P < 0.001$ for trend; **Fig. 5A**). These findings demonstrate that patients in the lowest quartile of serum DHEAS levels have the most rapid progression on AA, regardless of *PTEN* status, while those with DHEAS levels in the top 3 quartiles can be meaningfully stratified by *PTEN* status. In this small study WT MYC was also weakly correlated with longer survival (40 vs. 16 weeks, $P = 0.08$) while *TP53* status or the presence of *AR* mutation or amplification were not associated with progression (**Fig. 5A**).

As inhibition of AR signaling has been associated with reciprocal induction of PTEN signaling (19, 20), we determined if lower androgens were associated with PTEN loss. Median serum levels of T and DHT at baseline were numerically but not statistically lower in patients with *PTEN* loss versus WT *PTEN* ($P = 0.09$ and 0.084, respectively; Supplementary Fig. S7B), as were on-treatment levels of DHEAS in tissue ($P = 0.09$). Median serum levels of DHEAS and DHEA at baseline were also numerically lower in patients with *TP53* loss versus WT *TP53* ($P = 0.053$ and 0.047, respectively; Supplementary Fig. S7C). These observations suggest that while specific AR-independent tumor drivers such as *PTEN* and *TP53* may be selected to emerge in a low-androgen environment, a low-androgen environment is likely to promotes a more aggressive tumor biology by multiple mechanisms not limited to specific pathway alterations.

Association of *HSD3B1* genotype with steroid and abiraterone levels and radiographic PFS

The 1245C variant of *HSD3B1* produces a more stable enzyme, increasing conversion of DHEA to AED, a precursor of T and DHT (Supplementary Fig. S4), as well as increasing conversion of abiraterone to D4-abiraterone (21). Germline DNA testing identified 14 men who were homozygous WT (48%), 10 men who were heterozygous (34%), and 6 who were homozygous for the allelic variant (21%). Consistent with the impact of the variant on enhancing conversion of abiraterone to D4-abiraterone, serum levels of this metabolite were highest in subjects with two variant alleles (median 2.7 ng/mL) versus one variant allele (2.1 ng/mL) versus two WT alleles (1.2 ng/mL; ANOVA $P = 0.02$; Supplementary Fig. S8A). Serum levels of 3-keto-5α-abiraterone did not differ by *HSDB1* genotype, nor did levels of abiraterone metabolite in tissue (Supplementary Fig. S8A). There was no difference in serum or tissue-androgen levels based on *HSD3B1* status (including the five tissue samples with detectable levels of DHT; Supplementary Fig. S8B), nor in time-to-progression (Supplementary Fig. S8C).

Discussion

In this phase II study we demonstrate that in mCRPC AA plus prednisone decreases T levels in metastatic tissue biopsies to undetectable by 4 and 12 weeks of therapy, consistent with the predicted mechanism of activity. Steroid and abiraterone levels in serum and tissue remained stable at progression compared with earlier time points, consistent with prior reports regarding serum adrenal androgens (8), but demonstrating for the first time that tissue-androgen levels also remain unchanged at progression. Overall, these findings suggest that the development of resistance to AA plus prednisone is not accounted for by a decrease in serum or tissue drug levels below the levels originally achieved in response to therapy. Nor is it accounted for

by an increase in serum or intratumoral androgens above the levels originally achieved in response to AA plus prednisone. The observations that tumor steroid levels do not become reelevated at progression and that persistent serum DHEAS levels do not become undetectable after dose escalation of AA to 2,000 mg likely accounts for the lack of clinical response to high-dose AA at progression, now reported in two studies (22).

At baseline, serum levels of DHEAS and DHEA varied by over an order of magnitude (range 36–2,659 ng/mL) and demonstrated two patterns of response to treatment. While median levels of steroids downstream of CYP17A decreased by a similar order of magnitude in all patients, the subset of patients defined by higher serum DHEAS levels prior to therapy also had higher serum levels of other steroids at baseline; higher levels of DHEAS, AED, and ASD in pretreatment tissue biopsies; and maintained higher DHEAS levels in on-treatment serum samples and tissue biopsies. These observations demonstrate that serum DHEAS levels prior to therapy can distinguish patients with correspondingly lower or higher serum and tissue levels of all androgens and can identify those likely to maintain persistent serum and tissue DHEAS levels while on treatment with AA plus prednisone.

The correlation of low baseline with low on-treatment adrenal-androgen levels is of particular interest as lower adrenal androgens prior to therapy have been consistently associated with worse response to AA plus prednisone (13, 23–25). We show for the first time that this association with worse outcomes extends to low on-treatment level of DHEAS in serum and tissue, and with low adrenal androgens in pretreatment metastasis biopsies. At baseline, the association of worse response with lower levels was highly significant for DHEAS in serum ($P = 0.0018$) and for DHEAS and AED in pretreatment tissue biopsies ($P = 0.0003$ and $P = 0.0002$, respectively). On therapy, serum DHEAS in the lowest quartile at 4 and 8 weeks ($P = 0.0001$ and 0.024, respectively), as well as undetectable versus detectable DHEAS levels in metastatic biopsies taken at 4 and 12 weeks ($P = 0.023$ and $P = 0.04$, respectively) all associated with more rapid progression on AA therapy. These specific associations with DHEAS are consistent with the fact that DHEAS is the predominant steroid in serum and tissue prior to therapy, and remains the only steroid consistently present at measurable levels in metastatic tissue after AA therapy.

While response to AA is clearly linked with suppression of circulating and intratumor androgens, the paradoxical association of better outcomes with higher on-treatment androgen levels suggests that response to AA is not dictated solely by a pharmacodynamic effect on serum or tissue androgens, but may reflect an intrinsic resistance to AR-pathway therapy associated with tumor outgrowth in a low androgen microenvironment (26). These observations suggest that baseline serum androgen levels, by identifying patients with a more aggressive tumor biology that is less androgen dependent, may be prognostic as well as predictive of response to AR-pathway–directed therapy. As such, patients with higher androgens may have better survival independent of an effect of AA. This is consistent with the association of lower serum androgen levels with decreased survival in both the placebo and AA arms of the phase III study of AA plus prednisone in men with mCRPC (13), and with a recent meta-analysis demonstrating that PFS and OS were lower in patients with CRPC with lower versus higher T levels (27).

Importantly, the observation that lower androgen levels in CRPC associate with worse outcomes is not incompatible with data linking the achievement of lower T levels with improved time-to-progression in men with CSPC treated with ADT (28, 29). While time-to-development of CRPC may be delayed, CRPC tumors that emerge in patients with lower T levels (due to low adrenal contribution and/or optimally suppressed T levels while on ADT) are likely to represent a more aggressive, less androgen-dependent phenotype compared with tumors that emerge with more rapid kinetics in context of higher androgen levels (due to more robust adrenal contribution and/or suboptimally suppressed T levels). While this may not influence response to subsequent non–AR-specific agents such as docetaxel, it is likely to adversely influence response to next-generation AR-targeted therapy. This is consistent with findings in the meta-analysis discussed above, in which lower T levels were a consistently poor prognostic factor for OS in patients with CRPC treated with AR-targeting agents, but not in those treated with chemotherapy (27).

The significant variation in adrenal androgen levels is not well understood. Functional polymorphisms in genes encoding critical steroidogenic enzymes such as CYP17A, HSD3B1, SULT2A1, AKR1C3, SRD5A, and UGT2B17 influence enzyme activity and/or production of downstream steroids (21, 30–32). Population-based studies will be required to determine whether a composite haplotype of genes involved in adrenal androgen production exists that may account for the observed spectrum of serum androgen levels. Alternatively, the variability might reflect genetic variation in regulatory factors such as *CYB5A1, NR5A1* (also known as SF-1 or steroidogenic factor 1), or *MC2R* [the adrenocorticotropic hormone (ACTH) receptor] that are upstream of adrenal steroid synthesis (33–35).

We found no association of abiraterone levels with PSA decline or with time-to–radiographic progression, with nearly all patients having serum levels above the 8.4 ng/mL value previously proposed as a cutoff for PSA response (36). This contrasts with the observation of Friedlander and colleagues who found in a study of 41 men with mCRPC that patients who failed to show a PSA response to AA had lower abiraterone levels after 4 weeks and at progression (22). This difference may reflect variability in timing of the blood draws, which, while mandated before the daily dose, were not specifically recorded precluding correction for differences based on pharmacokinetics (18). However, our findings are consistent with the work of Smulewitz and colleagues, who also found no correlation between abiraterone levels and change in PSA in a study of 72 men with mCRPC randomized to standard or low-dose AA (37), as well as with an analysis performed by the FDA in which no association was found between trough abiraterone levels and OS (38).

The adrenal-permissive variant of *HSD3B1* (promotes conversion of AED and T to downstream androgens, and of abiraterone to D4-abiraterone and 3-keto-5α-abiraterone) has been consistently associated with more rapid progression on ADT (39), and potentially with worse outcomes in response to AA and enzalutamide in some but not all studies (40–43). Although we did find an association of *HSD3B1* status with D4-abiraterone (the immediate downstream product of *HSD3B1)*, we did not observe an association of *HSD3B1* genotype with response to abiraterone, nor the previously reported association with 3-keto-5α-abiraterone, potentially reflecting that serum levels were not corrected for differences based on pharmacokinetics. (18) However, we did observe that serum levels of 3-keto-5α-abiraterone above the median at weeks 4 and 8 were associated with a more rapid time-to-progression. These observations are consistent with the ability of this metabolite to act as an AR agonist, and suggest that dose escalation of AA may in fact be detrimental to patient outcomes. These findings provide support for the low-dose AA strategy proposed by Smulewitz (37), and provide impetus for clinical trials combining AA therapy with an SRD5A inhibitor to prevent conversion of D4-abiraterone to 5α-keto metabolite (44, 45).

NGS of CRPC tumors has identified aberrations in multiple genes including *AR, TP53, PTEN*, and *SPOP* which have been explored as predictive biomarkers of response to AR-pathway inhibition. In this small study we found no association of AR, TP53, or SPOP status with response to AA (46–48). In our cohort, WT PTEN was weakly associated with longer time-to-progression on AA plus prednisone, consistent with Ferraldeschi and colleagues who reported a retrospective study of 144 patients in which PTEN loss was associated with shorter OS (14 vs. 21 months; $P = 0.004$) and shorter duration of abiraterone treatment (24 vs. 28 weeks; $P = 0.009$; ref. 49). Moreover, whereas poor response to AA in men with the lowest serum DHEAS levels was not additionally influenced by PTEN status, in those with higher androgen levels WT PTEN versus PTEN loss conferred a significantly longer time-to-progression (61 vs. 33 weeks; $P = 0.02$). While our study is too small to meaningfully predict genomic alterations associated with response to AR-pathway inhibition, these data suggest that interpretation of tumor sequencing data may be more informative if analyzed in context of the risk conferred by low versus high serum androgen levels.

This study has several important limitations, including small sample size, that abiraterone and metabolite levels were not corrected for pharmacokinetic differences based on timing of trough blood draws, and that analyses were exploratory with no attempt to correct for multiple testing. As such, our observations must be considered hypothesis generating and require validation in larger data sets.

Our data show that higher circulating adrenal androgens in patients with CRPC are strongly associated with an androgen-rich tumor microenvironment before and during therapy with AA and prednisone, and suggest that ambient androgen levels in the castrate tumor microenvironment are an important determinant of prostate-tumor biology and response to therapy (13). Baseline and on-treatment androgen levels are likely to be important in the stratification and interpretation of trials evaluating AR-pathway–directed therapy. In particular, while addition of AA to enzalutamide did not prolong survival in metastatic CRPC (50), higher baseline DHEAS levels may distinguish a subset of patients who do benefit from dual-AR therapy. Conversely, patients with CRPC in the lowest quartile of serum DHEAS levels may warrant stratification to regimens that include non–AR-directed therapy. Whether adrenal androgens associate with response to AA in metastatic CSPC is unknown but requires exploration. Prospective studies evaluating baseline and on-treatment androgen levels as predictive biomarkers of response to AR-directed therapy are required to test these hypotheses.

Authors' Disclosures

E.A. Mostaghel reports grants from NIH and DOD during the conduct of the study; E.A. Mostaghel also reports grants from DOD and NIH, non-financial and other support from ESSA and Propella, and non-financial support from Orion outside the submitted work. B.T. Marck reports grants from NIH and DOD, as well as other support from Janssen during the conduct of the study. E.Y. Yu reports personal fees from Janssen, Clovis, AbbVie, Sanofi, AstraZeneca, Amgen, Exelixis, and Resverlogix; grants and personal fees from Advanced Accelerator Applications, Merck, Bayer, Pharmacyclics, Dendreon, and Seagen; and grants from Daiichi Sankyo, Taiho, Blue Earth Diagnostics, and Lantheus outside the submitted work. M.T. Schweizer reports grants from Janssen, DoD, PNW Prostate Cancer SPORE, BMS, Zenith Epigenetics, Merck, Immunomedics, Janssen, AstraZeneca, Pfizer, Madison Vaccines, F. Hoffmann-La Roche, Eli Lilly, Tmunity, and NCI during the conduct of the study, as well as grants from Elevate Bio outside the submitted work. H.H. Cheng reports grants from Janssen during the conduct of the study; H.H. Cheng also reports personal fees from AstraZeneca and UpToDate, as well as grants from Clovis Oncology, Astellas, Sanofi, Color Genomics, and Phosplatin outside the submitted work. P.W. Kantoff reports personal fees from Anji, Bavarian Nordic Immunotherapeutics, Bayer, Convergent Therapeutics, Candel, Context, DRGT, Genentech/Roche, Janssen, Merck, ImmunisAI, Progenity, SynDevRx, Tarveda, and Veru, as well as non-financial support from Cogent, Mirati, Placon, Prognomiq, SEER, and XLink outside the submitted work; in addition, H.H. Cheng is currently CEO of Convergent Therapeutics. M.-E. Taplin reports personal fees from Janssen, AstraZeneca, Clovis, Pfizer, Epizyme, Myovant, Constellation, Bayer, AbbVie, Astellas, and Arcus Bioscience during the conduct of the study. N. Sharifi reports grants from Astellas outside the submitted work; in addition, N. Sharifi has a patent for Cleveland Clinic and had a patent on HSD3B1 issued. P.S. Nelson reports personal fees from Astellas, Janssen, Bristol Myers Squibb, and Venable outside the submitted work. R.B. Montgomery reports grants from Janssen during the conduct of the study. No disclosures were reported by the other authors.

Authors' Contributions

E.A. Mostaghel: Conceptualization, resources, data curation, formal analysis, funding acquisition, methodology, writing–original draft, writing–review and editing. **B.T. Marck:** Data curation, formal analysis, investigation, methodology, writing–review and editing. **O. Kolokythas:** Resources, writing–review and editing. **F. Chew:** Resources, writing–review and editing. **E.Y. Yu:** Resources, writing–review and editing. **M.T. Schweizer:** Resources, writing–review and editing. **H.H. Cheng:** Resources, writing–review and editing. **P.W. Kantoff:** Resources, writing–review and editing. **S.P. Balk:** Resources, writing–review and editing. **M.E. Taplin:** Resources, writing–review and editing. **N. Sharifi:** Resources, methodology, writing–review and editing. **A.M. Matsumoto:** Resources, data curation, supervision, writing–review and editing. **P.S. Nelson:** Conceptualization, resources, funding acquisition, writing–review and editing. **R.B. Montgomery:** Conceptualization, resources, supervision, funding acquisition, writing–review and editing.

Acknowledgments

This work was supported by grants from DOD W81XWH-14-1-0004 (to E.A. Mostaghel); Pacific Northwest Prostate Cancer SPORE P50CA097186 (to E.A. Mostaghel, P.S. Nelson, R.B. Montgomery); P01 CA163227 (to E.A. Mostaghel, P.S. Nelson, S.P. Balk); R01 CA234715 (P.S. Nelson); R01 CA172382 and R01 CA236780 (both to N. Sharifi); and Department of Veterans Affairs Puget Sound Health Care System (to E.A. Mostaghel, A.M. Matsumoto). Funding of the clinical trial was provided by Janssen.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received May 18, 2021; revised July 9, 2021; accepted August 13, 2021; published first August 18, 2021.

References

1. Montgomery RB, Mostaghel EA, Vessella R, Hess DL, Kalhorn TF, Higano CS, et al. Maintenance of intratumoral androgens in metastatic prostate cancer: a mechanism for castration-resistant tumor growth. Cancer Res 2008;68:4447–54.
2. Mohler JL, Gregory CW, Ford OH 3rd, Kim D, Weaver CM, Petrusz P, et al. The androgen axis in recurrent prostate cancer. Clin Cancer Res 2004;10:440–8.
3. Stanbrough M, Bubley GJ, Ross K, Golub TR, Rubin MA, Penning TM, et al. Increased expression of genes converting adrenal androgens to testosterone in androgen-independent prostate cancer. Cancer Res 2006;66:2815–25.
4. Sharifi N. The 5alpha-androstanedione pathway to dihydrotestosterone in castration-resistant prostate cancer. J Investig Med 2012;60:504–7.
5. Taplin ME, Montgomery B, Logothetis CJ, Bubley GJ, Richie JP, Dalkin BL, et al. Intense androgen-deprivation therapy with abiraterone acetate plus leuprolide acetate in patients with localized high-risk prostate cancer: results of a randomized phase II neoadjuvant study. J Clin Oncol 2014;32:3705–15.
6. Tamae D, Mostaghel E, Montgomery B, Nelson PS, Balk SP, Kantoff PW, et al. The DHEA-sulfate depot following P450c17 inhibition supports the case for

AKR1C3 inhibition in high risk localized and advanced castration resistant prostate cancer. Chem Biol Interact 2015;234:332–8.
7. Attard G, Reid AH, Auchus RJ, Hughes BA, Cassidy AM, Thompson E, et al. Clinical and biochemical consequences of CYP17A1 inhibition with abiraterone given with and without exogenous glucocorticoids in castrate men with advanced prostate cancer. J Clin Endocrinol Metab 2012;97: 507–16.
8. Ryan CJ, Smith MR, Fong L, Rosenberg JE, Kantoff P, Raynaud F, et al. Phase I clinical trial of the CYP17 inhibitor abiraterone acetate demonstrating clinical activity in patients with castration-resistant prostate cancer who received prior ketoconazole therapy. J Clin Oncol 2010;28:1481–8.
9. Fizazi K, Scher HI, Molina A, Logothetis CJ, Chi KN, Jones RJ, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 2012;13:983–92.
10. Ryan CJ, Smith MR, de Bono JS, Molina A, Logothetis CJ, de Souza P, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 2013;368:138–48.
11. Mostaghel EA, Marck B, Plymate S, Vessella RL, Balk SP, Matsumoto AM, et al. Resistance to CYP17A1 inhibition with abiraterone in castration resistant prostate cancer: Induction of steroidogenesis and androgen receptor splice variants. Clin Cancer Res 2011;17:5913–25.
12. Reid AH, Attard G, Danila DC, Oommen NB, Olmos D, Fong PC, et al. Significant and sustained antitumor activity in post-docetaxel, castration-resistant prostate cancer with the CYP17 inhibitor abiraterone acetate. J Clin Oncol 2010;28:1489–95.
13. Ryan CJ, Molina A, Li J, Kheoh T, Small EJ, Haqq CM, et al. Serum androgens as prognostic biomarkers in castration-resistant prostate cancer: results from an analysis of a randomized phase III trial. J Clin Oncol 2013; 31:2791–8.
14. Mostaghel EA, Cho E, Zhang A, Alyamani M, Kaipainen A, Green S, et al. Association of tissue abiraterone levels and SLCO genotype with intraprostatic steroids and pathologic response in men with high-risk localized prostate cancer. Clin Cancer Res 2017;23:4592–601.
15. Pritchard CC, Salipante SJ, Koehler K, Smith C, Scroggins S, Wood B, et al. Validation and implementation of targeted capture and sequencing for the detection of actionable mutation, copy number variation, and gene rearrangement in clinical cancer specimens. J Mol Diagn 2014;16:56–67.
16. Hearn JWD, AbuAli G, Reichard CA, Reddy CA, Magi-Galluzzi C, Chang KH, et al. HSD3B1 and resistance to androgen-deprivation therapy in prostate cancer: a retrospective, multicohort study. Lancet Oncol 2016;17: 1435–44.
17. Petrylak DP, Ankerst DP, Jiang CS, Tangen CM, Hussain MH, Lara PN Jr, et al. Evaluation of prostate-specific antigen declines for surrogacy in patients treated on SWOG 99-16. J Natl Cancer Inst 2006;98:516–21.
18. Alyamani M, Emamekhoo H, Park S, Taylor J, Almassi N, Upadhyay S, et al. HSD3B1(1245A>C) variant regulates dueling abiraterone metabolite effects in prostate cancer. J Clin Invest 2018;128:3333–40.
19. Mulholland DJ, Tran LM, Li Y, Cai H, Morim A, Wang S, et al. Cell autonomous role of PTEN in regulating castration-resistant prostate cancer growth. Cancer Cell 2011;19:792–804.
20. Carver BS, Chapinski C, Wongvipat J, Hieronymus H, Chen Y, Chandarlapaty S, et al. Reciprocal feedback regulation of PI3K and androgen receptor signaling in PTEN-deficient prostate cancer. Cancer Cell 2011;19:575–86.
21. Chang K, Li R, Kuri B, Lotan Y, Roehrborn C, Liu J, et al. A gain-of-function mutation in DHT synthesis in castration-resistant prostate cancer. Cell 2013;154: 1074–84.
22. Friedlander TW, Graff JN, Zejnullahu K, Anantharaman A, Zhang L, Paz R, et al. High-dose abiraterone acetate in men with castration resistant prostate cancer. Clin Genitourin Cancer 2017;15:733–41.
23. Attard G, Reid AH, A'Hern R, Parker C, Oommen NB, Folkerd E, et al. Selective inhibition of CYP17 with abiraterone acetate is highly active in the treatment of castration-resistant prostate cancer. J Clin Oncol 2009;27: 3742–8.
24. Kim W, Zhang L, Wilton JH, Fetterly G, Mohler JL, Weinberg V, et al. Sequential use of the androgen synthesis inhibitors ketoconazole and abiraterone acetate in castration-resistant prostate cancer and the predictive value of circulating androgens. Clin Cancer Res 2014;20:6269–76.
25. Suzuki K, Sakamoto M, Terakawa T, Furukawa J, Harada K, Hinata N, et al. Serum DHEA-S is a predictive parameter of abiraterone acetate in patients with castration-resistant prostate cancer. Anticancer Res 2018;38:5929–35.
26. Valcamonico F, Ferrari L, Consoli F, Amoroso V, Berruti A. Testosterone serum levels and prostate cancer prognosis: the double face of Janus. Future Oncol 2014; 10:1113–5.
27. Miura N, Mori K, Mostafaei H, Quhal F, Sari Motlagh R, Abufaraj M, et al. Prognostic value of testosterone for the castration-resistant prostate cancer patients: a systematic review and meta-analysis. Int J Clin Oncol 2020;25: 1881–91.
28. Toren P, Hoffman A, Ding K, Joncas FH, Turcotte V, Caron P, et al. Serum sex steroids as prognostic biomarkers in patients receiving androgen deprivation therapy for recurrent prostate cancer: a post hoc analysis of the PR.7 trial. Clin Cancer Res 2018;24:5305–12.
29. Klotz L, O'Callaghan C, Ding K, Toren P, Dearnaley D, Higano CS, et al. Nadir testosterone within first year of androgen-deprivation therapy (ADT) predicts for time to castration-resistant progression: a secondary analysis of the PR-7 trial of intermittent versus continuous ADT. J Clin Oncol 2015;33: 1151–6.
30. Wilborn TW, Lang NP, Smith M, Meleth S, Falany CN. Association of SULT2A1 allelic variants with plasma adrenal androgens and prostate cancer in African American men. J Steroid Biochem Mol Biol 2006;99:209–14.
31. Shiota M, Fujimoto N, Yokomizo A, Takeuchi A, Kashiwagi E, Dejima T, et al. The prognostic impact of serum testosterone during androgen-deprivation therapy in patients with metastatic prostate cancer and the SRD5A2 polymorphism. Prostate Cancer Prostatic Dis 2016;19:191–6.
32. Nadeau G, Bellemare J, Audet-Walsh E, Flageole C, Huang SP, Bao BY, et al. Deletions of the androgen-metabolizing UGT2B genes have an effect on circulating steroid levels and biochemical recurrence after radical prostatectomy in localized prostate cancer. J Clin Endocrinol Metab 2011;96:E1550–7.
33. Stark K, Straub RH, Rovenský J, Blažičková S, Eiselt G, Schmidt M. CYB5A polymorphism increases androgens and reduces risk of rheumatoid arthritis in women. Arthritis Res Ther 2015;17:56.
34. Schimmer BP, Cordova M, Tsao J, Frigeri C. SF1 polymorphisms in the mouse and steroidogenic potential. Endocr Res 2002;28:519–25.
35. Liu ZL, He B, Fang F, Tang CY, Zou LP. Genetic polymorphisms of MC2R gene associated with responsiveness to adrenocorticotropic hormone therapy in infantile spasms. Chin Med J 2008;121:1627–32.
36. Carton E, Noe G, Huillard O, Golmard L, Giroux J, Cessot A, et al. Relation between plasma trough concentration of abiraterone and prostate-specific antigen response in metastatic castration-resistant prostate cancer patients. Eur J Cancer 2017;72:54–61.
37. Szmulewitz RZ, Peer CJ, Ibraheem A, Martinez E, Kozloff MF, Carthon B, et al. Prospective international randomized phase II study of low-dose abiraterone with food versus standard dose abiraterone in castration-resistant prostate cancer. J Clin Oncol 2018;36:1389–95.
38. US Food and Drug Administration. Clinical pharmacology and biopharmaceutics review(s) abiraterone acetate. APPLICATION NUMBER: 202379Orig1s000. 2011; Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202379Orig1s000PharmR.pdf.
39. Thomas L, Sharifi N. Germline HSD3B1 genetics and prostate cancer outcomes. Urology 2020;145:13–21.
40. Hahn AW, Gill DM, Nussenzveig RH, Poole A, Farnham J, Cannon-Albright L, et al. Germline variant in HSD3B1 (1245 A >C) and response to abiraterone acetate plus prednisone in men with new-onset metastatic castration-resistant prostate cancer. Clin Genitourin Cancer 2018;16:288–92.
41. Lu C, Terbuch A, Dolling D, Yu J, Wang H, Chen Y, et al. Treatment with abiraterone and enzalutamide does not overcome poor outcome from metastatic castration-resistant prostate cancer in men with the germline homozygous HSD3B1 c.1245C genotype. Ann Oncol 2020;31:1178–85.
42. Khalaf DJ, Aragón IM, Annala M, Lozano R, Taavitsainen S, Lorente D, et al. HSD3B1 (1245A>C) germline variant and clinical outcomes in metastatic castration-resistant prostate cancer patients treated with abiraterone and enzalutamide: results from two prospective studies. Ann Oncol 2020;31:1186–97.
43. Shiota M, Narita S, Akamatsu S, Fujimoto N, Sumiyoshi T, Fujiwara M, et al. Association of missense polymorphism in HSD3B1 with outcomes among men with prostate cancer treated with androgen-deprivation therapy or abiraterone. JAMA Netw Open 2019;2:e190115.
44. McKay RR, Werner L, Mostaghel EA, Lis R, Voznesensky O, Zhang Z, et al. A phase II trial of abiraterone combined with dutasteride for men with metastatic castration-resistant prostate cancer. Clin Cancer Res 2017;23:935–45.
45. Li Z, Alyamani M, Li J, Rogacki K, Abazeed M, Upadhyay SK, et al. Redirecting abiraterone metabolism to fine-tune prostate cancer anti-androgen therapy. Nature 2016;533:547–51.

46. Conteduca V, Wetterskog D, Sharabiani MTA, Grande E, Fernandez-Perez MP, Jayaram A, et al. Androgen receptor gene status in plasma DNA associates with worse outcome on enzalutamide or abiraterone for castration-resistant prostate cancer: a multi-institution correlative biomarker study. Ann Oncol 2017;28: 1508–16.
47. Boysen G, Rodrigues DN, Rescigno P, Seed G, Dolling D, Riisnaes R, et al. SPOP-mutated/CHD1-deleted lethal prostate cancer and abiraterone sensitivity. Clin Cancer Res 2018;24:5585–93.
48. De Laere B, Oeyen S, Mayrhofer M, Whitington T, van Dam PJ, Van Oyen P, et al. TP53 outperforms other androgen receptor biomarkers to predict abiraterone or enzalutamide outcome in metastatic castration-resistant prostate cancer. Clin Cancer Res 2019;25:1766–73.
49. Ferraldeschi R, Nava Rodrigues D, Riisnaes R, Miranda S, Figueiredo I, Rescigno P, et al. PTEN protein loss and clinical outcome from castration-resistant prostate cancer treated with abiraterone acetate. Eur Urol 2015;67: 795–802.
50. Morris MJ, Heller G, Bryce AH, Armstrong AJ, Beltran H, Hahn OM, et al. Alliance A031201: a phase III trial of enzalutamide (ENZ) versus enzalutamide, abiraterone, and prednisone (ENZ/AAP) for metastatic castration resistant prostate cancer (mCRPC). J Clin Oncol 2019;37:5008.

Niraparib in patients with metastatic castration-resistant prostate cancer and DNA repair gene defects (GALAHAD): a multicentre, open-label, phase 2 trial

*Matthew R Smith, Howard I Scher, Shahneen Sandhu, Eleni Efstathiou, Primo N Lara Jr, Evan Y Yu, Daniel J George, Kim N Chi, Fred Saad, Olof Ståhl, David Olmos, Daniel C Danila, Gary E Mason, Byron M Espina, Xin Zhao, Karen A Urtishak, Peter Francis, Angela Lopez-Gitlitz, Karim Fizazi, on behalf of the GALAHAD investigators**

Lancet Oncol 2022; 23: 362–73

Published Online February 4, 2022 https://doi.org/10.1016/S1470-2045(21)00757-9

*The full list of GALAHAD investigators is provided in the appendix (p 3)

Massachusetts General Hospital Cancer Center, Boston, MA, USA (Prof M R Smith MD); **Harvard Medical School, Boston, MA, USA** (Prof M R Smith); **Memorial Sloan Kettering Cancer Center, New York, NY, USA** (Prof H I Scher MD, D C Danila MD); **Peter MacCallum Cancer Center and University of Melbourne, Melbourne, VIC, Australia** (S Sandhu MD); **Houston Methodist Cancer Center, Houston, TX, USA** (E Efstathiou MD); **University of California Davis Comprehensive Cancer Center, Sacramento, CA, USA** (Prof P N Lara Jr MD); **Division of Medical Oncology, University of Washington, Seattle, WA, USA** (Prof E Y Yu MD); **Duke Cancer Institute, Durham, NC, USA** (Prof D J George MD); **University of British Columbia, BC Cancer Vancouver Center, Vancouver, BC, Canada** (Prof K N Chi MD); **Department of Urology, Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada** (Prof F Saad MD); **Department of Oncology, Skane University Hospital, Lund, Sweden** (O Ståhl MD); **Hospital Universitario 12 de Octubre, Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas12), Madrid, Spain** (D Olmos MD); **Janssen Research & Development, Spring House, PA, USA** (G E Mason MD, K A Urtishak PhD); **Janssen Research & Development, Los Angeles, CA, USA** (B M Espina BS, A Lopez-Gitlitz MD); **Janssen Research & Development, San Francisco, CA, USA**

Summary

Background Metastatic castration-resistant prostate cancers are enriched for DNA repair gene defects (DRDs) that can be susceptible to synthetic lethality through inhibition of PARP proteins. We evaluated the anti-tumour activity and safety of the PARP inhibitor niraparib in patients with metastatic castration-resistant prostate cancers and DRDs who progressed on previous treatment with an androgen signalling inhibitor and a taxane.

Methods In this multicentre, open-label, single-arm, phase 2 study, patients aged at least 18 years with histologically confirmed metastatic castration-resistant prostate cancer (mixed histology accepted, with the exception of the small cell pure phenotype) and DRDs (assessed in blood, tumour tissue, or saliva), with progression on a previous next-generation androgen signalling inhibitor and a taxane per Response Evaluation Criteria in Solid Tumors 1.1 or Prostate Cancer Working Group 3 criteria and an Eastern Cooperative Oncology Group performance status of 0–2, were eligible. Enrolled patients received niraparib 300 mg orally once daily until treatment discontinuation, death, or study termination. For the final study analysis, all patients who received at least one dose of study drug were included in the safety analysis population; patients with germline pathogenic or somatic biallelic pathogenic alterations in *BRCA1* or *BRCA2* (*BRCA* cohort) or biallelic alterations in other prespecified DRDs (non-*BRCA* cohort) were included in the efficacy analysis population. The primary endpoint was objective response rate in patients with *BRCA* alterations and measurable disease (measurable *BRCA* cohort). This study is registered with ClinicalTrials.gov, NCT02854436.

Findings Between Sept 28, 2016, and June 26, 2020, 289 patients were enrolled, of whom 182 (63%) had received three or more systemic therapies for prostate cancer. 223 (77%) of 289 patients were included in the overall efficacy analysis population, which included *BRCA* (n=142) and non-*BRCA* (n=81) cohorts. At final analysis, with a median follow-up of 10·0 months (IQR 6·6–13·3), the objective response rate in the measurable *BRCA* cohort (n=76) was 34·2% (95% CI 23·7–46·0). In the safety analysis population, the most common treatment-emergent adverse events of any grade were nausea (169 [58%] of 289), anaemia (156 [54%]), and vomiting (111 [38%]); the most common grade 3 or worse events were haematological (anaemia in 95 [33%] of 289; thrombocytopenia in 47 [16%]; and neutropenia in 28 [10%]). Of 134 (46%) of 289 patients with at least one serious treatment-emergent adverse event, the most common were also haematological (thrombocytopenia in 17 [6%] and anaemia in 13 [4%]). Two adverse events with fatal outcome (one patient with urosepsis in the *BRCA* cohort and one patient with sepsis in the non-*BRCA* cohort) were deemed possibly related to niraparib treatment.

Interpretation Niraparib is tolerable and shows anti-tumour activity in heavily pretreated patients with metastatic castration-resistant prostate cancer and DRDs, particularly in those with *BRCA* alterations.

Funding Janssen Research & Development.

Introduction

Patients with metastatic castration-resistant prostate cancer who have progressed on a next-generation androgen signalling inhibitor and taxane chemotherapy (docetaxel, cabazitaxel, or both) have few treatment options.[1,2] DNA repair gene defects (DRDs), seen in approximately 12–23% of tumours in patients with metastatic prostate cancer when considering both germline and somatic alterations,[3–5] are associated with cancer development, aggressiveness, and progression.[6] These DRD-altered tumours are not only frequent in metastatic disease, but are also associated with poor prognosis and potential resistance to systemic therapies.[7] Developing more effective treatments to improve survival for these patients is therefore a critical unmet need.

Cancers with DRDs, particularly those with defects in homologous recombination repair, are highly sensitive to the blockade of DNA single-strand break repair via inhibition of the PARP family of nuclear proteins, which

Research in context

Evidence before this study

At the time that the GALAHAD study was designed, docetaxel and the androgen signalling inhibitors abiraterone acetate and enzalutamide were the only established treatment options for patients with metastatic castration-resistant prostate cancer, but there remained a subset of patients who either did not initially respond or became refractory to these agents and for whom no approved therapeutic options were available. Given that genomic instability is a hallmark of cancer that has been documented in this patient population, we evaluated the medical literature by searching PubMed from database inception up to Aug 31, 2016, with (castration) AND (resistant) AND ("prostatic neoplasm" OR "prostate cancer") AND ("genomic instability" OR "DNA repair" OR "DNA repair defect") as search terms of interest with no additional restrictions (eg, to English language publications only). The search yielded 33 results. Only two of these were clinical trial publications, which presented results from an early phase 1 study of veliparib and the phase 2 TOPARP study of olaparib—both PARP inhibitors—in this disease setting. Veliparib was reported to have low efficacy, but the high response rate observed among patients with specified DNA repair gene defects (DRDs) in the TOPARP study provided a compelling rationale for assessing the clinical activity and safety of other such agents in a genetically selected patient population. Coauthors of the current study also contributed appropriate citations of importance that were not detected by the original search strategy or that were found in subsequent literature, with an emphasis on randomised clinical trials, systematic reviews, meta-analyses, and prospective observational studies. Taken together, the findings indicated that PARP inhibitors show notable activity in cancers with DRDs. In articles published since the GALAHAD study was initiated, further clinical activity has since been reported in metastatic castration-resistant prostate cancers with selected DRDs for the PARP inhibitors olaparib, rucaparib, and talazoparib (for which key primary publications are cited in the present work), but not yet for niraparib, which is also a potent and highly selective PARP inhibitor with established efficacy and tolerability in other cancers.

Added value of this study

To our knowledge, the GALAHAD study is the first to show the anti-tumour activity of niraparib in patients with metastatic castration-resistant prostate cancer and DRDs who previously progressed on both androgen signalling inhibitors and taxanes, with notable activity particularly in the cohort of patients with defects in *BRCA1* or *BRCA2*.

Implications of all the available evidence

This final analysis of the GALAHAD study suggests that in patients with heavily pretreated metastatic castration-resistant disease, niraparib could offer promising clinical activity with a manageable safety profile. These findings motivate the further assessment of niraparib alone or in combination with other agents to improve treatment options and underscore the importance of biological disease profiling in informing treatment decisions.

are involved in single-strand DNA break repair.[8] PARP inhibitors, such as olaparib, rucaparib, and talazoparib, have been studied in patients with metastatic castration-resistant prostate cancer and DRDs in previous phase 2 and 3 studies.[9–13] Olaparib is approved in the EU for *BRCA1*-mutated or *BRCA2*-mutated metastatic castration-resistant prostate cancer[14] and by the US Food and Drug Administration (FDA) for patients with metastatic castration-resistant prostate cancer and DRDs progressing after treatment with enzalutamide, abiraterone, or both,[15] whereas rucaparib is approved for patients with *BRCA1*-mutated or *BRCA2*-mutated metastatic castration-resistant prostate cancer who have been treated with an androgen signalling inhibitor therapy and a taxane.[16]

Niraparib, a potent and highly selective inhibitor of PARP-1 and PARP-2, is approved by the FDA for the maintenance treatment of select patient populations with ovarian, fallopian tube, and primary peritoneal cancers.[17,18] Here, we report the final anti-tumour activity and safety results of a multicentre, open-label, phase 2 study of niraparib in patients with metastatic castration-resistant prostate cancer and tumour DRDs, whose disease had progressed on androgen signalling inhibitor therapy and taxane chemotherapy (docetaxel, cabazitaxel, or both).

Methods

Study design and participants

GALAHAD is an open-label, phase 2 study at 115 hospitals or health-care centres in 15 countries (appendix pp 8–9), which consisted of the following phases: prescreening, screening, treatment, follow-up, and long-term extension.

Male patients aged at least 18 years with histologically confirmed metastatic castration-resistant prostate cancer (mixed histology was acceptable, with the exception of the small cell pure phenotype, which was excluded) were eligible if they had a predefined DRD and disease progression on an androgen signalling inhibitor and taxane chemotherapy (docetaxel, cabazitaxel, or both). Disease progression was defined as progression of metastatic prostate cancer in the setting of castrate levels of testosterone of up to 50 ng/dL on a gonadotropin-releasing hormone analogue or with history of bilateral orchiectomy at study entry, with progression specifically defined as prostate-specific antigen (PSA) progression or radiographic progression of soft tissue by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 or bone disease by Prostate Cancer Working Group 3 (PCWG3) criteria.[19,20] Patients were also required to have an Eastern Cooperative Oncology Group (ECOG)

(X Zhao PhD); **Janssen Research & Development, New Brunswick, NJ, USA** (P Francis MD); **Institut Gustave Roussy, University of Paris Saclay, Villejuif, France** (Prof K Fizazi MD)

Correspondence to:
Dr Matthew R Smith, Massachusetts General Hospital Cancer Center, Boston, MA 02114
smith.matthew@mgh.harvard.edu

See **Online** for appendix

performance status of 2 or less. Patients with measurable and non-measurable disease were enrolled. Exclusion criteria included previous treatment with a PARP inhibitor or platinum-based chemotherapy regimen, and a known history or current diagnosis of myelodysplastic syndrome or acute myeloid leukaemia. The full eligibility criteria are available in the protocol (appendix).

All patients provided written informed consent. Independent ethics committees or institutional review boards of each participating institution approved this study. The study was conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki. The study protocol is available in the appendix.

Procedures

Patients were prescreened using a blood sample (Resolution Bioscience, Kirkland, WA, USA) or tumour tissue sample (Foundation Medicine, Cambridge, MA, USA[21]) for evaluation of DRD alterations. The Resolution Bioscience assay, Resolution HRD, is a targeted hybrid capture, next-generation sequencing assay that detects single-nucleotide variants, indels, and copy number variation (including homozygous deletions) in genes involved in homologous recombination repair using cell-free DNA from plasma. The specific genes of interest for DRD consisted of eight candidates: *ATM*, *BRCA1*, *BRCA2*, *BRIP1*, *CHEK2*, *FANCA*, *HDAC2*, and *PALB2*. In addition, three genes that are commonly mutated in metastatic castration-resistant prostate tumours were evaluated: *AR*, *CDKN2A*, and *TP53*. This Resolution Bioscience assay can also identify patients with monoallelic and biallelic pathogenic alterations in the genes of interest. Patients were eligible to enter the screening phase if a deleterious germline or somatic alteration was found in at least one of the following genes: *ATM*, *BRCA1*, *BRCA2*, *BRIP1*, *CHEK2*, *FANCA*, *HDAC2*, and *PALB2*. Patients were considered DRD-positive if they had an alteration with known pathogenic consequences including homozygous deletions; rearrangements; and nonsense, missense, frame-shift, and splice-site mutations. After the assay was developed to distinguish between biallelic and monoallelic DRD, patients who had been enrolled with monoallelic or non-pathogenic DRD were excluded from the final analysis according to an approved protocol amendment (amendment 3; October, 2017). As such, only patients with germline pathogenic or biallelic pathogenic alterations in *BRCA1* or *BRCA2* (*BRCA* cohort) or other prespecified non-*BRCA* genes (non-*BRCA* cohort) were included in the final analysis. Additional details on testing methods are available in the appendix (p 4).

All patients received niraparib 300 mg orally in the form of 100 mg capsules (Quotient Sciences, Boothwyn, PA, USA) starting on day 1 of cycle 1 (once daily dosing, with a cycle defined as 28 days) until treatment discontinuation due to disease progression, unacceptable toxicity or adverse events, diagnosis of myelodysplastic syndrome or acute myeloid leukaemia, investigator decision in the best interest of the patient, patient withdrawal of consent, death, or study termination. Monitoring for the need of dose adjustments or interruptions (eg, with laboratory measurements) was at the discretion of the investigator, based on the severity of the adverse events experienced. Patients who were not surgically castrated continued regularly prescribed gonadotropin-releasing hormone analogue.

During the treatment phase, study visits occurred weekly for the first month, biweekly for the second month, and monthly thereafter. CT or MRI and ^{99m}technetium bone scans were performed during screening, every 8 weeks for 24 weeks, and then every 12 weeks thereafter. Circulating tumour cell (CTC) counts were assessed at every cycle until cycle 7 and then at the end-of-treatment visit. PSA assessments were done every 4 weeks until cycle 7 and then every three cycles thereafter.

The follow-up phase began after completion of the treatment phase. If a patient discontinued treatment without radiographic progression, imaging was done every 12 weeks (or within 2 weeks before or after this timepoint) until radiographic progression was documented. The long-term extension phase began after completion of the primary analysis, at which point patients could elect to discontinue treatment or continue niraparib until disease progression. Throughout the study, adverse events were evaluated and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03 or later). Safety evaluations included incidence, severity, and types of adverse events, as well as deaths. Adverse events were classified as treatment-emergent adverse events if they were reported on or after the date of first dose until 30 days (inclusive) after the last dose of study drug. Drug-related adverse events were determined by investigators if they were considered related to the study drug. Appropriate supportive measures to address adverse events could be administered at the discretion of investigators per institutional standards of care. A full schedule of study assessments and procedures is available in the protocol in the appendix.

Outcomes

The primary endpoint was investigator-assessed objective response rate (defined as the proportion of patients with a confirmed partial response or complete response as defined by RECIST version 1.1,[19] according to the sum of target tumour lesion diameters, with no evidence of bone progression on bone scan per PCWG3 criteria[20]) in patients with *BRCA* alterations and measurable disease (the measurable *BRCA* cohort). The primary endpoint was amended early on in this study (amendment 2; January, 2017) from a composite response endpoint to objective response rate to comply with feedback from health authorities, and hence the primary efficacy analysis included only these participants with measurable disease; additional details regarding this amendment are available in the study protocol in the appendix. Patients with non-measurable disease were still included in the

study to increase the size of the safety population and to assess the activity of niraparib in this population.

Secondary efficacy endpoints were objective response rate in patients with non-*BRCA* alterations (*ATM*, *BRIP1*, *CHEK2*, *FANCA*, *HDAC2*, and *PALB2*) and measurable disease; CTC response (CTC0) defined as CTC=0 per 7·5 mL blood at 8 weeks post-baseline in patients with CTC count greater than 0 (1 or more) at baseline;[22,23] overall survival (time from enrolment to death from any cause); radiographic progression-free survival (time from enrolment to radiographic progression or death from any cause, whichever occurred first); time from enrolment to radiographic progression; time to PSA progression (defined as time from enrolment to first date of documented PSA progression based on PCWG3 criteria); time to symptomatic skeletal event (defined as time from enrolment to tumour-related spinal cord compression, radiotherapy to bone to relieve skeletal symptoms, surgery to bone or need for tumour-related orthopaedic surgical intervention, or symptomatic or pathological fracture); duration of objective response (defined as time from complete response or partial response to radiographic progression of disease, unequivocal clinical progression, or death, whichever occurred first); and safety. With the exception of objective response rate in patients with non-*BRCA* alterations and measurable disease, all secondary endpoints were assessed in both the *BRCA* and non-*BRCA* populations.

Prespecified exploratory endpoints included the composite response rate, defined as either an objective response for patients with measurable disease, CTC conversion (defined as CTC count ≥5 per 7·5 mL blood at baseline and <5 per 7·5 mL blood post-therapy nadir), or at least a 50% decline in PSA (PSA_{50}). Both CTC conversion and PSA_{50} were also assessed separately as prespecified exploratory analyses.

Statistical analysis

Statistical analysis followed Simon's two-stage design for phase 2, single-arm clinical trials.[24] Specifically for the non-*BRCA* cohort, a futility analysis for objective response rate based on this design was implemented, in which Simon's stage 1 was assessed after approximately 14 patients with measurable disease were evaluated for objective response rate with at least one post-treatment scan and a confirmatory scan; enrolment was to be terminated for this cohort if two or fewer responses were observed in the first stage. Otherwise, enrolment was specified to proceed to the second stage with a total of 45 patients enrolled for the two stages combined, and the null hypothesis was to be rejected if ten or more responses were observed. For the primary endpoint, the null hypothesis of an objective response rate of 15% or less was tested against the alternate hypothesis of an objective response rate of 32% or higher. With approximately 120 patients with biomarker-positive measurable disease (75 *BRCA* and 45 non-*BRCA*) planned for enrolment, the study had more than 90% power to show that the lower limit of the 95% CI for the primary endpoint of objective response rate exceeded 15% in the measurable *BRCA* cohort. Activity of niraparib was to be declared if the lower bound of the two-sided 95% exact CI for objective response rate was higher than 15% in this cohort. For the secondary endpoint of objective response rate in patients with non-*BRCA* alterations, the null hypothesis of an objective response rate of 15% or less was tested against the alternate hypothesis of an objective response rate of 32% or higher, with a one-sided α of 0·05 and power of 80%.

Objective response in soft tissue disease was evaluated in both *BRCA* and non-*BRCA* patients with measurable disease within the efficacy analysis population of patients who fulfilled the final biomarker assay criteria for this study; however, as prespecified, the primary endpoint was specifically evaluated in the cohort of *BRCA* patients with measurable disease, and the final primary endpoint analysis was planned for approximately 6 months after the last patient with measurable disease in the *BRCA* cohort was enrolled. For analysis of objective response rate, patients who discontinued treatment before any efficacy assessments were considered non-responders; patients with no imaging available for a particular study visit were considered not evaluable for that visit, and patients without valid baseline data were considered not evaluable. Anti-tumour activity, such as PSA response, CTC conversion or response, and composite response rate, was analysed separately for the *BRCA* and non-*BRCA* cohorts, with corresponding criteria for identification of non-responders and non-evaluable patients based on discontinuation or availability of laboratory measurements. Response rates were calculated along with exact two-sided 95% CIs. Time-to-event endpoints were summarised by Kaplan-Meier curves with median times and 95% CIs, as well as descriptive event-free rates analysed as prespecified. Analyses of additional study outcomes, such as the prespecified calculation of treatment compliance in the form of relative dose intensity, are described in further detail in the appendix (p 4).

Post-hoc analyses included objective response rate by baseline characteristics of interest (such as in subgroups of patients with visceral disease at baseline, patients who experienced stable disease for more than 6 months, or patients with three or more previous lines of therapy), specific evaluation of stable disease (defined as neither sufficient decrease in target lesions to qualify for partial response, nor sufficient increase to qualify for progressive disease, with respect to smallest sum of target lesion diameters while on study), and biomarker analyses for non-DRD alterations of interest (*AR* and *TP53* alteration) were also done using the available data. For the post-hoc analysis of patients with *AR* and *TP53* alterations, differences in objective response rates were assessed using Pearson's χ^2 test and p values were adjusted using false discovery rate correction for multiple testing (Benjamini-Hochberg procedure).

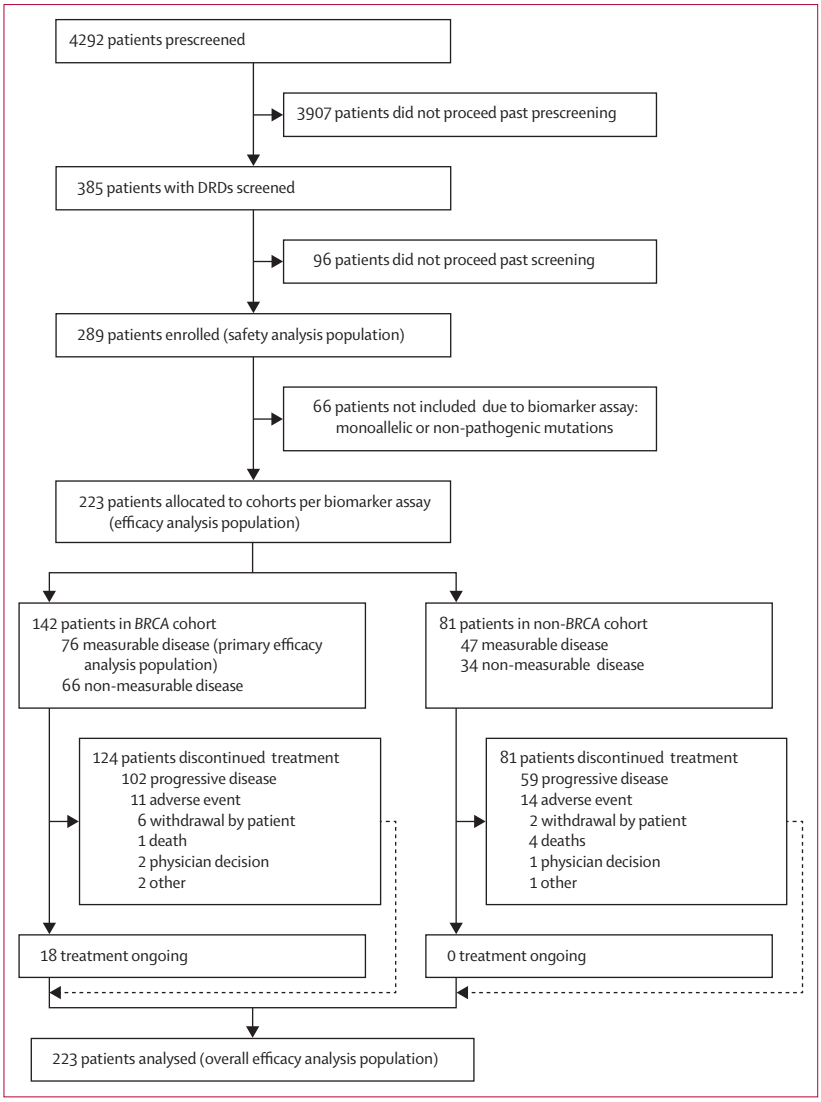


Figure 1: **Trial profile**
DRD=DNA repair gene defect.

Safety and treatment compliance were analysed in the safety analysis population (ie, all patients who received at least one dose of the study drug). Adverse events and serious adverse events were reported and summarised. Sensitivity analyses with censoring rules were done if warranted. Additional details from the statistical analysis plan are available in the appendix. Statistical analyses were performed using SAS (version 15.1).

This study is registered with ClinicalTrials.gov, NCT02854436, and with the European Clinical Trials database, EudraCT 2016-002057-38).

Role of the funding source

The sponsor and employees of the sponsor of this study participated in the study design, data collection, data analysis, and data interpretation, with writing and editorial assistance also funded by the sponsor. All authors participated in the writing process and provided critical input.

Results

385 patients were screened for this study; of these, 289 (75%) patients were enrolled between Sept 28, 2016, and June 26, 2020. All 289 patients were included in the safety analysis population, and 223 (77%) of 289 patients were included in the efficacy analysis population, based on DRD eligibility from the validated biomarker assay (142 with *BRCA* alterations [139 biallelic, three monoallelic germline pathogenic] and 81 with biallelic non-*BRCA* alterations; figure 1). 66 (23%) of 289 patients with monoallelic or non-pathogenic DRD from the safety analysis were not included in the final efficacy analysis. Additional information on the prescreening results is available in the appendix (p 5). For patients with measurable disease, 76 with *BRCA* alterations (primary efficacy population) and 47 with non-*BRCA* alterations were enrolled, which fulfilled the numbers required per study sample size estimation for evaluation of objective response rate. The types and frequencies of genotypes observed in the efficacy analysis are reported in the appendix (p 10).

Based on the Simon's two-stage design, enrolment proceeded through both stages to fulfill the estimated sample size requirements. At the clinical cutoff date of Jan 26, 2021, 271 (94%) of 289 patients had discontinued treatment, with reasons summarised in the appendix (p 11). Seven (9%) of 76 patients in the primary efficacy cohort (patients with *BRCA* alterations and measurable disease) discontinued therapy before their first study evaluation due to progressive disease (n=4), urosepsis leading to death (n=1), or withdrawal of consent (n=1 due to fear of COVID-19; n=1 received radium-223 due to bone disease burden). The median treatment duration was 6·5 months (IQR 3·3–9·4) in the *BRCA* cohort and 3·6 months (1·8–5·6) in the non-*BRCA* cohort. Dose adjustments and interruptions are summarised in the appendix (p 12), with most treatment dose reductions occurring due to an adverse event.

Patients were heavily pretreated and showed advanced disease in both the *BRCA* and non-*BRCA* populations (table 1). Nearly all patients had bone metastases and, in the primary efficacy population (the measurable *BRCA* cohort), a notable proportion of patients had visceral disease, including liver and lung metastases, as well as many patients having nodal disease.

At baseline, 182 (63%) of 289 patients in the safety analysis population had received at least three previous systemic therapies for metastatic prostate cancer; 94 (33%) had received two previous androgen signalling inhibitor therapies, and 107 (37%) had received two previous taxane-based chemotherapies. The demographics and baseline characteristics of the safety analysis population are presented in the appendix (p 13). The final activity results

for the overall *BRCA* cohort (with a median follow-up of 10·1 months [IQR 7·5–13·4]) are shown in tables 2 and 3 and the appendix (pp 6, 7, 14).

The primary endpoint, objective response rate per protocol in the measurable *BRCA* cohort, was met in 26 of 76 patients (34·2%, 95% CI 23·7–46·0; table 2) with a median follow-up of 10·0 months (IQR 6·6–13·3). Of the 76 patients in the measurable *BRCA* cohort, 35 (46%) had at least a 30% decrease of maximum change from baseline in the sum of longest target lesion diameters relative to baseline (appendix p 6). Median duration of objective response was 5·55 months (95% CI 3·91–7·20; table 3); eight (31%) of 26 responses were ongoing at the time of data cutoff.

Figure 2 and table 3 present radiographic progression-free survival, with 87 (61%) events at the time of data cutoff, and overall survival, with 88 (62%) events in the overall *BRCA* cohort. 12-month event-free survival in the overall *BRCA* cohort was 56·4% (95% CI 47·2–64·6), and 24-month event-free survival was 15·2% (7·7–25·1). Approximately a quarter of patients reached CTC0 (table 3). 85 (60%) of 142 patients in the *BRCA* cohort and 42 (55%) of 76 patients in the measurable *BRCA* cohort experienced PSA progression, and 46 (32%) of 142 patients and 23 (30%) of 76 patients had a documented symptomatic skeletal event in these cohorts, respectively.

The exploratory endpoint of composite response rate in the overall *BRCA* cohort is also presented in table 3. More than 40% of patients in the overall *BRCA* cohort had PSA_{50} and CTC conversion (also exploratory), and approximately two thirds of evaluable patients experienced a decrease in PSA levels from baseline (table 3; appendix p 7). Similar outcomes in composite response rate were obtained in the *BRCA* cohort for patients with measurable and non-measurable disease (appendix p 14).

Of note, two patients (both with biallelic alterations) in the measurable *BRCA* cohort had a complete response. One patient with visceral (adrenal) and nodal disease at baseline maintained the complete response for 9·7 months, and a second patient with nodal disease at baseline experienced a complete response that persisted for 9·5 months based on imaging, despite having received only 2·1 months of treatment that was discontinued due to an adverse event of anaemia (grade 3). In a post-hoc analysis, of the 30 patients in the measurable *BRCA* cohort who had visceral disease at baseline, 11 (37%) had an objective response. Furthermore, a post-hoc analysis of the 20 patients who experienced stable disease for more than 6 months in this study showed that 14 (70%) were in the *BRCA* cohort. 16 (21%) of the 76 patients in the measurable *BRCA* cohort continued treatment after radiographic progression with no unequivocal clinical progression because they were considered to still be benefiting from therapy.

For the measurable non-*BRCA* cohort (n=47; median follow-up of 8·6 months [IQR 4·8–14·0]), objective response rate per protocol and median duration of response (none of which are ongoing) are shown in table 2. An objective response was recorded in five of 47 patients (10·6%; 95% CI 3·5–23·1) in this cohort.

The corresponding maximum changes in the sum of target tumour lesion diameters from baseline in the

	BRCA cohort (n=142)	Measurable *BRCA* cohort (n=76)	Non-*BRCA* cohort (n=81)	Measurable non-*BRCA* cohort (n=47)
Age, years	67·0 (63·0–73·0)	66·0 (62·0–73·0)	70·0 (66·0–75·0)	71·0 (59·0–86·0)
Bodyweight, kg	82·7 (15·5)	80·5 (13·4)	79·9 (16·1)	77·6 (13·0)
Race				
White	101 (71%)	57 (75%)	54 (67%)	33 (70%)
Asian	9 (6%)	6 (8%)	6 (7%)	3 (6%)
Black or African American	5 (4%)	3 (4%)	0	0
Other	3 (2%)	0	2 (2%)	0
Multiple	1 (1%)	0	2 (2%)	1 (2%)
Not reported	11 (8%)	5 (7%)	8 (10%)	4 (9%)
Unknown	12 (8%)	5 (7%)	9 (11%)	6 (13%)
PSA at baseline, ng/mL	141·5 (41·0–512·4)	197·0 (40·1–653·9)	161·7 (43·7–611·1)	196·0 (43·7–662·3)
Patients with alterations in a single gene*				
BRCA1	4 (3%)	3 (4%)	..	..
BRCA2	127 (89%)	69 (91%)	..	..
ATM	..	..	37 (46%)	21 (45%)
BRIP1	..	..	1 (1%)	1 (2%)
CHEK2	..	..	5 (6%)	2 (4%)
FANCA	..	..	18 (22%)	10 (21%)
HDAC2	..	..	8 (10%)	5 (11%)
PALB2	..	..	0	0
ECOG performance status score				
0	48 (34%)	25 (33%)	18 (22%)	9 (19%)
1	78 (55%)	44 (58%)	47 (58%)	27 (57%)
2	16 (11%)	7 (9%)	16 (20%)	11 (23%)
Extent of disease progression at study entry				
Bone	127 (89%)	61 (80%)	79 (98%)	45 (96%)
Visceral	33 (23%)	30 (39%)	20 (25%)	16 (34%)
Liver	24 (17%)	23 (30%)	13 (16%)	12 (26%)
Lung	15 (11%)	13 (17%)	10 (12%)	7 (15%)
Lymph node	79 (56%)	67 (88%)	39 (48%)	33 (70%)
Soft tissue	22 (15%)	21 (28%)	16 (20%)	15 (32%)
Disease status				
Measurable	76 (54%)	76 (100%)	47 (58%)	47 (100%)
Non-measurable	66 (46%)	0	34 (42%)	0
Gleason score at diagnosis				
<8	39/135 (29%)	20/73 (27%)	26/77 (34%)	15/43 (35%)
≥8	96/135 (71%)	53/73 (73%)	51/77 (66%)	28/43 (65%)
Previous therapies for prostate cancer†				
Two	59 (42%)	29 (38%)	22 (27%)	10 (21%)
Three	54 (38%)	31 (41%)	31 (38%)	18 (38%)
Four	21 (15%)	12 (16%)	19 (23%)	12 (26%)
Five	7 (5%)	3 (4%)	9 (11%)	7 (15%)
Six	1 (1%)	1 (1%)	0	0

(Table 1 continues on next page)

	BRCA cohort (n=142)	Measurable *BRCA* cohort (n=76)	Non-*BRCA* cohort (n=81)	Measurable non-*BRCA* cohort (n=47)
(Continued from previous page)				
Previous androgen signalling inhibitor therapies				
One	97 (68%)	51 (67%)	45 (56%)	23 (49%)
Two	44 (31%)	25 (33%)	31 (38%)	21 (45%)
Three	1 (1%)	0	5 (6%)	3 (6%)
Previous taxane-based chemotherapies				
One	100 (70%)	51 (67%)	41 (51%)	21 (45%)
Two	42 (30%)	25 (33%)	40 (49%)	26 (55%)

Data are reported as median (IQR), mean (SD), n (%), or n/N (%). The measurable *BRCA* cohort (n=76) is the primary efficacy population and the *BRCA* and non-*BRCA* cohorts combined (n=223) is the overall efficacy analysis population. PSA=prostate-specific antigen. ECOG=Eastern Cooperative Oncology Group. *All patients with *PALB2* had co-occurring alterations and are thus not listed here; patient numbers and percentages might not add up to 100% because some patients had more than one gene alteration and are thus not listed here. †Number of androgen signalling inhibitors, taxane-based chemotherapies, cytotoxic chemotherapies, and other therapies received; specifically, previous therapies could include taxane-based chemotherapy for metastatic prostate cancer with evidence of disease progression, or next-generation androgen signalling inhibitor therapy for either metastatic prostate cancer with evidence of disease progression or non-metastatic castration-resistant prostate cancer with evidence of subsequent metastasis.

Table 1: **Baseline characteristics of patients in the overall efficacy analysis population**

	Measurable *BRCA* cohort* (n=76)	Measurable non-*BRCA* cohort† (n=47)
Objective response rate	26 (34·2%; 23·7–46·0)	5 (10·6%; 3·5–23·1)
Complete response	2 (3%)	0
Partial response	24 (32%)	5 (11%)

Data are n (%; 95% CI) or n (%). *Primary efficacy analysis cohort. †Objective response rate in measurable non-*BRCA* patients was a secondary efficacy endpoint.

Table 2: **Objective response rates**

overall non-*BRCA* cohort (n=81) are presented in the appendix (p 6).

Figure 2 and table 3 also present radiographic progression-free survival in the non-*BRCA* cohort, with 57 (70%) events at the time of data cutoff, and overall survival, with 65 (80%) events. 12-month event-free survival was 41·3% (95% CI 30·0–52·2), and 24-month event-free survival was 11·1% (4·4–21·2). Fewer than 10% of patients reached CTC0 in this cohort; 39 (48%) of 81 patients had PSA progression, and 19 (23%) of 81 patients had a documented symptomatic skeletal event.

The exploratory endpoint of composite response rate in the non-*BRCA* cohort is also presented in table 3, and the maximum change in PSA from baseline is presented in the appendix (p 7). Response by either PSA_{50} or CTC conversion (also exploratory) among non-*BRCA* patients with non-measurable disease is provided in the appendix (p 14).

In post-hoc analyses of the non-*BRCA* cohort, two (13%) of 16 patients with visceral disease and four (80%) of five patients who had received three or more lines of therapy experienced an objective response in the non-*BRCA* cohort; six patients in this cohort experienced stable disease for more than 6 months. 15 (32%) of 47 patients continued treatment after radiographic progression with no unequivocal clinical progression.

Of note, 11 (8%) of 142 patients in the *BRCA* cohort and seven (9%) of 81 patients in the non-*BRCA* cohort had co-expression of two or more eligible DRD biomarkers. Moreover, in addition to being DRD-positive, 162 (74%) of 220 patients with available plasma DNA results had alterations in the *AR* gene and 49 (22%) of 220 had alterations in *TP53*, of whom 42 (19%) had both *TP53* and *AR* alterations. These additional alterations in plasma DNA were similarly distributed between the *BRCA* and non-*BRCA* cohorts, and no substantial difference in objective response rate was observed in subgroups of patients with or without co-occurring alterations (appendix pp 15–16).

Safety results are summarised in table 4 and the appendix (pp 17–25, 28–30). Almost all patients in the safety population experienced at least one treatment-emergent adverse event. The most common adverse events (of any grade) were nausea (169 [58%] of 289), anaemia (156 [54%]), and vomiting (111 [38%]). Of the grade 3 or worse treatment-emergent adverse events reported in 217 (75%) of 289 patients, most were haematological, with both the most common grade 3 or worse adverse events overall and grade 3 or worse adverse events of special interest being anaemia (95 [33%] of 289), thrombocytopenia (47 [16%]), and neutropenia (28 [10%]). These events were manageable with one or more of: treatment interruptions, dose reductions, or supportive measures such as blood transfusions. One patient experienced neutropenic sepsis. The most common non-haematological grade 3–4 treatment-emergent adverse events were fatigue and nausea. 134 (46%) of 289 patients had at least one serious treatment-emergent adverse event, with haematological events being the most common (17 [6%] of 289 with thrombocytopenia and 13 [4%] of 289 with anaemia; appendix pp 21–23). Similarly, of 43 (15%) of 289 patients with drug-related serious treatment-emergent adverse events, the most common were thrombocytopenia (four [3%] of 142 in the *BRCA* cohort and seven [9%] of 81 in the non-*BRCA* cohort) and anaemia (three [2%] of 142 in the *BRCA* cohort and three [4%] of 81 in the non-*BRCA* cohort; appendix p 24). The most common adverse events overall by *BRCA* and non-*BRCA* cohorts are also summarised in the appendix (p 20).

Estimated relative dose intensities are presented in the appendix (pp 26–27), including a breakdown of relative dose intensities in responders versus non-responders in the primary efficacy analysis population (appendix p 26). In the safety population, 128 (44%) of 289 patients had an adverse event leading to a dose reduction; consistent with the aforementioned findings, 87 (68%) of 128 patients had haematological events

	BRCA cohort (n=142)	Measurable *BRCA* cohort (n=76)	Non-*BRCA* cohort (n=81)
CTC response*, n/N (%)	31/131 (24%)	18/71 (25%)	6/71 (8%)
Overall survival, months	13·01 (11·04–14·29)	10·87 (9·49–13·77)	9·63 (8·05–13·44)
Radiographic progression-free survival, months	8·08 (5·55–8·38)	5·52 (5·29–7·59)	3·71 (1·97–5·49)
Time to radiographic progression, months	8·08 (5·75–8·97)	5·55 (5·36–8·08)	3·78 (2·00–5·55)
Time to PSA progression, months	5·13 (4·60–5·59)	5·55 (4·60–8·31)	3·65 (2·83–3·71)
Time to symptomatic skeletal event, months	13·80 (10·41–NE)	13·80 (9·07–NE)	10·35 (8·18–NE)
Duration of objective response, months	6·28 (3·65–9·23)	5·55 (3·91–7·20)	5·16 (2·14–NE)
Composite response rate†, n/N (%; 95% CI)	82/142 (58%; 49·2–66·0)	46/76 (61%; 48·7–71·6)	12/81 (15%; 7·9–24·5)
CTC conversion‡, n/N (%; 95% CI)	55/117 (47%; 37·7–56·5)	28/64 (44%; 31·4–56·7)	9/60 (15%; 7·1–26·6)
PSA_{50}, n/N (%; 95% CI)	61/142 (43%; 34·7–51·5)	31/76 (41%; 29·7–52·7)	4/81 (5%; 1·4–12·2)

Data are median (95% CI) unless otherwise indicated. CTC=circulating tumour cell. PSA=prostate-specific antigen. NE=not estimable. PSA_{50}=at least 50% decline in prostate-specific antigen. *Defined per protocol and statistical analysis plan as CTC=0 per 7·5 mL blood at 8 weeks post-baseline in patients with baseline CTC count >0. †Defined as an objective response for patients with measurable disease, CTC conversion (defined as CTC count ≥5 per 7·5 mL blood at baseline and <5 per 7·5 mL blood post-therapy nadir), or PSA_{50}. ‡Among patients with baseline CTC count ≥5.

Table 3: **Secondary and exploratory efficacy endpoints**

(appendix p 28), which were manageable with one or more of the following: dose reductions, interruptions, or appropriate supportive measures (administered at the discretion of investigators per institutional standards of care). Among patients evaluated for anti-tumour activity, 70 (95%) of 74 patients with dose reductions in the *BRCA* cohort and 37 (93%) of 40 patients with dose reductions in the non-*BRCA* cohort had dose reductions due to adverse events versus other reasons; 103 (46%) of 223 patients received at least one transfusion (platelets or packed red blood cells), and the incidence of transfusions was similar between the *BRCA* and non-*BRCA* cohorts (data not shown). Other supportive measures included colony-stimulating factors, which were administered to 12 (4%) of 289 patients, and erythropoietin, which was administered to 15 (5%) of 289 patients. 37 (13%) of 289 patients were deemed to have discontinued treatment due to drug-related toxicities (treatment-emergent adverse events deemed related to study drug). The most common drug-related toxicities leading to discontinuation were thrombocytopenia (in seven patients with *BRCA* alterations and three patients with non-*BRCA* alterations) and anaemia (in six patients with *BRCA* alterations and one patient with non-*BRCA* alteration; appendix p 25).

Adverse events leading to death are summarised in the appendix (p 29). Of the 16 deaths related to adverse events, two events (one patient with urosepsis in the *BRCA* cohort and one patient with sepsis in the non-*BRCA* cohort) were deemed possibly related to niraparib treatment. 208 (72%) of 289 patients died during the study; reasons for deaths are summarised in the appendix (p 30). The only sensitivity analysis warranted was for COVID-19, but there was only one patient with a COVID-19-related adverse event (non-serious) and one death due to COVID-19 in this study (appendix p 30).

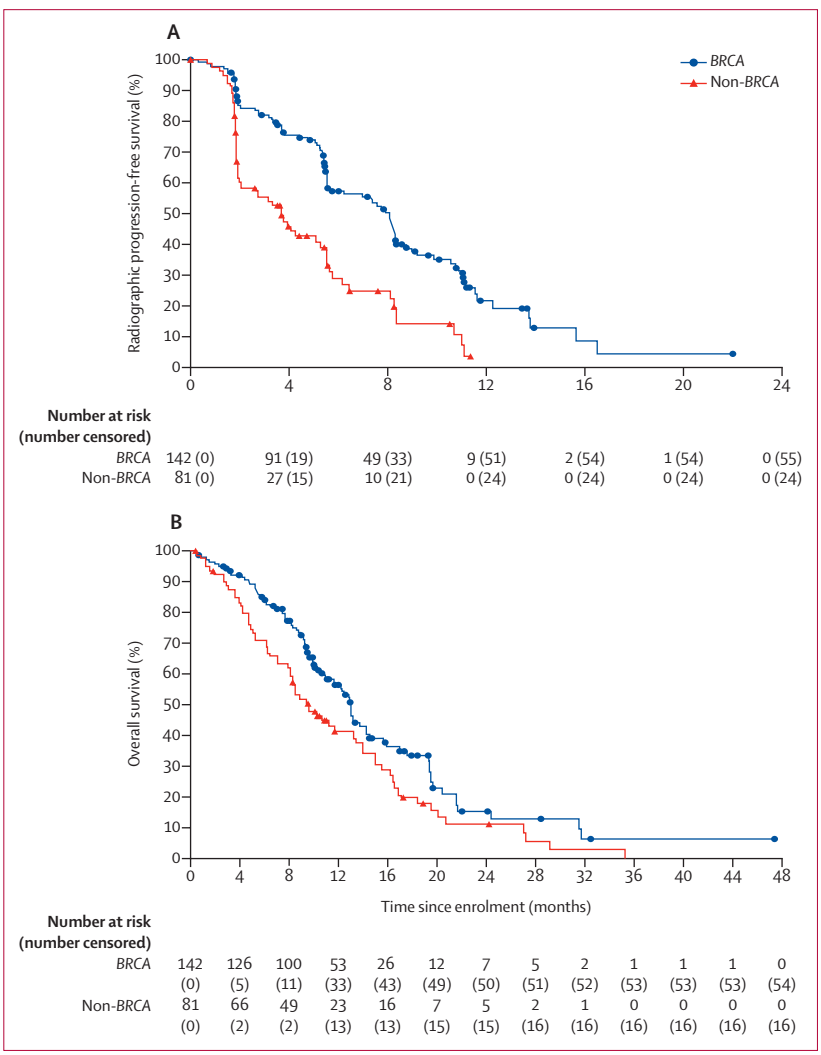


Figure 2: **Radiographic progression-free survival (A) and overall survival (B) in the *BRCA* and non-*BRCA* cohorts**
Symbols represent censored patients.

	Grade 1–2	Grade 3	Grade 4	Grade 5
Nausea	154 (53%)	15 (5%)	0	0
Vomiting	101 (35%)	10 (3%)	0	0
Constipation	95 (33%)	5 (2%)	1 (<1%)	0
Fatigue	87 (30%)	19 (7%)	0	0
Decreased appetite	85 (29%)	8 (3%)	0	0
Anaemia	61 (21%)	92 (32%)	2 (1%)	1 (<1%)
Thrombocytopenia	52 (18%)	24 (8%)	23 (8%)	0
Back pain	51 (18%)	13 (4%)	0	0
Arthralgia	38 (13%)	6 (2%)	0	0
Asthenia	37 (13%)	11 (4%)	0	0
Neutropenia	27 (9%)	17 (6%)	11 (4%)	0
Bone pain	23 (8%)	9 (3%)	0	0
Hypertension	22 (8%)	12 (4%)	0	0
Blood alkaline phosphatase increased	15 (5%)	11 (4%)	0	0
Stomatitis	15 (5%)	6 (2%)	0	0
Leukopenia	14 (5%)	11 (4%)	3 (1%)	0
γ-glutamyl transferase increased	13 (4%)	11 (4%)	1 (<1%)	0
Lymphopenia	11 (4%)	12 (4%)	1 (<1%)	0
Hypophosphataemia	7 (2%)	6 (2%)	1 (<1%)	0
Spinal cord compression	1 (<1%)	7 (2%)	0	0
General physical health deterioration	1 (<1%)	7 (2%)	1 (<1%)	4 (1%)

Data are shown as n (%). A total of 288 patients had one or more recorded treatment-emergent adverse events. Data are presented for grade 1–2 treatment-emergent adverse events with a combined incidence of ≥20% or any higher-grade (grade 3–5) treatment-emergent adverse events with an incidence of ≥2%.

Table 4: **Treatment-emergent adverse events in the safety analysis set (n=289)**

Discussion

The results of this multicentre, open-label, phase 2 study establish the anti-tumour activity of niraparib in patients with metastatic castration-resistant prostate cancer and DRDs who have progressed on both androgen signalling inhibitors and taxanes. Treatment with niraparib was manageable, and adverse events observed were consistent with the known safety profile of niraparib, with no new safety signals.

The activity of niraparib in the measurable *BRCA* cohort is notable given the heavily pretreated, end-stage patient population with few therapeutic options. These findings are especially remarkable considering the high percentage of patients with visceral metastasis, in particular to the liver, which is strongly associated with poor survival;[25] the high percentage of patients with three or more lines of previous therapy; and that some patients in the *BRCA* cohort even achieved a complete response. Further evidence of benefit was shown by the proportion of patients experiencing stabilisation of disease for more than 6 months in both the *BRCA* and non-*BRCA* cohorts, which is a clinically meaningful finding given this heavily pretreated advanced disease state. Also notable was that patients in both cohorts, some with multiple poor prognostic features, continued to derive clinical benefit from niraparib after radiographic progression (in line with the importance of considering the totality of a patient's disease before discontinuing a drug rather than strictly at the first evidence of progression in any site, as recommended by PCWG3[21]). Objective response rate, median radiographic progression-free survival and overall survival, and composite response rate were greater in the *BRCA* cohort than in the non-*BRCA* cohort, including a median radiographic progression-free survival time that was approximately double that in the non-*BRCA* cohort. Interestingly, our exploratory endpoint of composite response rate was largely similar between the subgroups of patients with measurable versus non-measurable disease in both cohorts (particularly in the *BRCA* cohort). Taken together, these results extend the evidence on the activity of PARP inhibitors in patients with metastatic castration-resistant prostate cancer and DRD-altered tumours whose disease has progressed on approved life-prolonging therapies, and also highlight the importance of biological profiling of an individual patient's disease in metastatic castration-resistant prostate cancer.[8,21] Of note, to our knowledge, this trial is the first to prospectively test the CTC0 endpoint, which has been shown to strongly associate with survival.[22]

The dose of niraparib used in this study (300 mg oral; once daily dosing) was chosen based on the previously evaluated pharmacokinetics, clinical activity, and safety profile of niraparib and is the approved dose for patients with ovarian cancer.[17,26] As expected, grade 3 or worse treatment-emergent adverse events were largely haematological and manageable with supportive measures (such as blood transfusions and growth factor treatment), dose interruptions, and dose reductions. Rates of treatment interruptions and reductions were higher than the previously reported rates for other PARP inhibitors.[9–13] This finding is consistent with the more advanced disease stage of patients in the GALAHAD trial, who had all progressed on androgen signalling inhibitor therapy and taxane chemotherapy and also tended to be on later lines of therapy, with the majority having received three or more lines of previous therapy. Moreover, the present study applied more stringent dose interruption criteria (for example, skipping a dose was also considered a dose interruption). Thus, the finding that at least half of the patients in both the *BRCA* and non-*BRCA* cohorts maintained the full dose (300 mg) of niraparib throughout the study supports the overall tolerability of this regimen. Relative dose intensity was also generally high, including in the primary efficacy cohort, and was higher for those who had an objective response in that cohort compared with those who did not.

The clinical activity of niraparib shown in this study's specific patient population (noting particular activity observed in the *BRCA* cohort) can be further contextualised by results of studies of other PARP inhibitors that point to a benefit for both minimally and heavily pretreated patients with metastatic castration-resistant prostate cancer and particular DRD alterations. Of note, in the phase 3 PROfound study that evaluated patients treated with the PARP inhibitor olaparib versus those treated with the

physician's choice of an androgen signalling inhibitor, olaparib treatment resulted in a median radiographic progression-free survival of 7·4 months versus 3·6 months (hazard ratio 0·34, 95% CI 0·25–0·47; p<0·001), median overall survival of 19·1 months versus 14·7 months (0·69, 0·50–0·97; p=0·02 at final analysis), and confirmed objective response rate of 33% (28 of 84) versus 2% (one of 43; odds ratio 20·86, 95% CI 4·18–379·18; p<0·001) compared with the control treatment in a cohort of patients with alterations in *BRCA1, BRCA2,* or *ATM*.[10,11] Rucaparib, which was investigated in the phase 2 TRITON-2 study, led to an objective response rate of 47·5% and a median time to PSA progression of 6·5 months, with a better response seen in patients with *BRCA* alterations compared with those with alterations in other genes such *ATM* or *CDK12*.[12,13] In the phase 2 TALAPRO-1 study, patients with certain gene alterations reported to sensitise to PARP inhibitors were enrolled and treated with talazoparib. The objective response rate was 29·8% (31 of 104; 95% CI 21·2–39·6) with talazoparib treatment after a median follow-up of 16·4 months.[9]

The limitations of the present study include that some patients developed progressive disease before completing their first disease evaluation, consistent with the advanced stage and aggressiveness of the disease in the enrolled population. Additionally, tissue-based assays rely on sufficient high-quality biopsy samples, which might be difficult to obtain, and further challenges ensue when archival samples are found to be unsuitable or unavailable for analysis. In this study, a commercially available tissue-based assay was initially used to select patients, but due to the aforementioned challenges, a blood-based assay was subsequently implemented, with early prescreening rates and biomarker logic finalisation then addressed during a brief study pause. As such, a notable number of patients in GALAHAD were prescreened using blood-based assay. Such assays could offer valuable data, especially for metastatic prostate cancer for which tumour biopsies are challenging to acquire and biopsies are largely limited to bone that has considerable issues with the quality of materials. However, liquid biopsies also have limitations. Given the lack of parallel next-generation sequencing of corresponding white blood cells in this study, clonal haematopoietic alterations of indeterminate potential could have presented as a biological confounding factor.[27] Additionally, blood-based assays might show false negative results in blood samples with low plasma circulating tumour DNA content, especially for mutations that are difficult to detect such as homozygous deletions. Conversely, circulating tumour DNA assays could select for patients with higher percentages of circulating tumour DNA, which was previously found to be a predictive factor for a poorer prognosis.[28] Nevertheless, the number of patients enrolled for efficacy evaluation in GALAHAD (n=223 with specifically germline pathogenic or biallelic DRD alterations, of a total of 4218 with any biomarker sample submitted) represents an incidence of DRD alterations that is within expectations. Finally, 22% of the GALAHAD study population had *TP53* alterations, which are also associated with overall poor prognosis.

Additional studies, including those designed to evaluate niraparib-based regimens in appropriate biomarker-identified populations at earlier stages of disease, are underway to expand on the present findings. The phase 3 MAGNITUDE study is evaluating niraparib in combination with abiraterone acetate plus prednisone as first-line therapy in patients with metastatic castration-resistant disease with or without DRD.[29] The phase 3 AMPLITUDE study will also evaluate niraparib in combination with abiraterone acetate plus prednisone in a biomarker-selected population with metastatic castration-sensitive disease.[30]

In conclusion, these results suggest that niraparib has promising clinical activity with a manageable safety profile when administered as a monotherapy for treatment-refractory metastatic castration-resistant prostate cancer with *BRCA* alterations or select non-*BRCA* alterations. Such findings underscore the need for and importance of molecular testing to inform management along with continued research to establish treatment paradigms with appropriately targeted therapies for patients with prostate cancer. Efforts to investigate and better understand predictive markers and signatures of both response and resistance to treatment with PARP inhibitors such as niraparib are needed to guide therapy selection and optimise treatment outcomes.

Contributors

All authors in their role as GALAHAD study investigators or Janssen Research & Development investigators contributed to study design, study conduct, data analysis, and data interpretation. All authors participated in drafting and revising the manuscript and approved the final version before submission. MRS, GEM, and XZ verified all data. All authors had full access to all data for the study and had final responsibility for the decision to submit for publication.

Declaration of interests

MRS has received grants or contracts to their institution from Bayer, Janssen, Pfizer, AstraZeneca, and Lilly; has received consulting fees from Astellas Pharma, Novartis, Janssen, AstraZeneca, Bayer, Lilly, and Pfizer; and has participated on data safety monitoring boards, advisory boards, or both for Janssen, Pfizer, and AstraZeneca. HIS has a leadership role in Asterias Biotherapeutics; holds stock and other ownership interests in Asterias Biotherapeutics; received grants or contracts to their institution from Epic Sciences, Illumina, Menarini Silicon Biosystems, ThermoFisher, and AIQ Pharma; provided consulting to Ambry Genetics Corporation/Konica Minolta, Amgen (uncompensated), Bayer, ESSA Pharma (uncompensated), Menarini Silicon Biosystems (uncompensated), Pfizer, Sun Pharmaceuticals, and WCG Oncology; has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Sidney Kimmel Cancer Center—Jefferson Health; has received support for attending meetings or travel from Amgen, Bayer, ESSA Pharma, Menarini Silicon Biosystems, Epic Sciences, Pfizer, WCG Oncology, and Phosplatin; has patents planned, issued, or pending via their institution with BioNTech, Elucida Oncology, MabVax Therapeutics, and Y-mAbs Therapeutics; and has other financial or non-financial interests in Elsevier, Prostate Cancer Foundation (via institution), National Cancer Institute (via institution), Department of Defense (via institution), MabVax Therapeutics, and BioNTech. SS has received grants from Amgen, Advanced Accelerator Applications (a Novartis company), Merck Sharp & Dohme,

AstraZeneca, and Genentech; has received grants and personal fees from AstraZeneca, Bristol Myers Squibb, and Merck Sharp & Dohme; and participated on a data safety monitoring board for Advanced Accelerator Applications (a Novartis company). EE has received grants or contracts, consulting fees, and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Sanofi, Astellas, Pfizer, Myovant, Merck Sharp & Dohme, AstraZeneca, and Novartis, and has participated on data safety monitoring boards, advisory boards, or both for Sanofi, Astellas, Pfizer, Myovant, Merck Sharp & Dohme, AstraZeneca, and Novartis. PNL Jr has received grants or contracts from Janssen to their institution. EYY has received grants or contracts from Bayer, Dendreon, Merck Sharp & Dohme, Seagen, Taiho, Blue Earth, and Lantheus; and has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Bayer, Clovis, Janssen, Merck Sharp & Dohme, Seagen, Sanofi, AbbVie, Advanced Accelerator Applications (a Novartis company), and Exelixis. DJG has received grants or contracts to their institution from Astellas, Bristol Myers Squibb, Calithera, Exelixis, Janssen, Novartis, Pfizer, and Sanofi; has received consulting fees from Astellas, AstraZeneca, Bayer, Bristol Myers Squibb, Constellation, Exelixis, Flatiron, IdeoOncology, Janssen, Merck, Myovant Sciences, Physician Education Resource, Pfizer, PlatformQ, Propella, RevHealth, Sanofi, Seattle Genetics, WebMD, and Xcures; has received payment or honoraria for lectures, presentation, speakers bureaus, manuscript writing, or educational events from Bayer, EMD Serono, Exelixis, Ipsen, Michael J Hennessey, Pfizer, Sanofi, UroGPO, and UroToday; has received payment for expert testimony from Wilmer Hale Attorneys; has received support for attending meetings or travel from Bayer, Exelixis, Sanofi, and UroToday; has participated on data safety monitoring boards, advisory boards, or both for Astellas, AstraZeneca, Janssen, and Modra; and holds a leadership or fiduciary role in the American Association for Cancer Research (senior editor), AstraZeneca (CAPI-281 study coordinator), Bristol Myers Squibb (study coordinator), Capio Biosciences (scientific advisory board), Millennium Medical Publishing (co-editor-in-chief, *Clinical Advances in Hematology & Oncology*), NCI Genitourinary (study coordinator), Nektar Therapeutics (study coordinator), and Pfizer (study coordinator). KNC has received grants or contracts to their institution from Janssen, AstraZeneca, Merck, Novartis, and Point Biopharma; has received consulting fees from Astellas, AstraZeneca, Janssen, Merck Sharp & Dohme, Novartis, Point Biopharma, and Roche; and has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Astellas, Janssen, Merck Sharp & Dohme, AstraZeneca, and Novartis. FS has received grants or contracts, consulting fees, payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events, and has received equipment, materials, drugs, medical writing, gifts, or other services from Janssen, Astellas, AstraZeneca, Bayer, Bristol Myers Squibb, Myovant, Sanofi, Novartis, and Pfizer; and has participated on data safety monitoring boards, advisory boards, or both for Janssen, Astellas, AstraZeneca, Bayer, Bristol Myers Squibb, Myovant, Sanofi, Novartis, and Pfizer. DO has received grants or contracts from AstraZeneca, Bayer, and Janssen; has received consulting fees from Clovis, Daiichi Sankyo, AstraZeneca, Bayer, Roche, Merck Sharp & Dohme, and Janssen; has received support for attending meetings or travel from AstraZeneca, Janssen, and Roche; and has participated on data safety monitoring boards, advisory boards, or both for Janssen, AstraZeneca, and Bayer. DCD has received consulting fees from Angle, Axiom, Janssen, Astellas, Medivation, Pfizer, Genzyme, and Agensys; and has other financial or non-financial interests (research support) in the US Department of Defense, the American Society of Clinical Oncology, the Prostate Cancer Foundation, Stand Up to Cancer, Janssen, Astellas, Medivation, Agensys, Genentech, and CreaTV. GEM, BME, KAU, PF, and AL-G are employees of Janssen Research & Development. GEM and PF own stocks with Janssen. XZ was an employee of Janssen at the time of this study. KAU has been listed as an inventor on a patent as an employee of Janssen Research & Development. KF has received consulting fees from AAA, Astellas, AstraZeneca, Bayer, Novartis, Janssen, Amgen, Pfizer, Orion, Curevac, and Sanofi; has received payment or honoraria from lectures, presentations, speakers bureaus, manuscript writing, or educational events from Astellas, AstraZeneca, Bayer, Janssen, Novartis, Merck Sharp & Dohme, Bristol Myers Squibb, and Orion; and has participated on data safety monitoring boards, advisory boards, or both for Astellas, AstraZeneca, Bayer, Novartis, Janssen, Amgen, Pfizer, Sanofi, Orion, and Curevac. OS declares no competing interests.

Data sharing

The full study protocol is available in the appendix. The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through the Yale Open Data Access Project site at http://yoda.yale.edu. De-identified patient-level data will be made available to qualified researchers upon request, after signing of a data transfer agreement with Janssen Research & Development. Requests for data sharing, including a research proposal, can also be made to the corresponding author.

Acknowledgments

This study was funded by Janssen Research & Development. We thank the patients who participated in this study, along with their families, and the study teams who were involved at each participating institution. Statistical analysis support was provided by Eugene Zhu and George Wang of Janssen Research & Development (Raritan, NJ, USA). Medical writing and editorial assistance were provided by Michelle Kwon and Danyang Zhou of Cello Health Communications/MedErgy (Yardley, PA, USA), which was provided in accordance with Good Publication Practice (GPP3) guidelines and funded by Janssen Research & Development. HIS is in receipt of the following National Instititutes of Health (NIH) grants: NIH/National Cancert Institute (NCI) Prostate SPORE Grant P50-CA92629 and NIH/NCI Cancer Center Support Grant P30 CA008748.

References

1 Gillessen S, Attard G, Beer TM, et al. Management of patients with advanced prostate cancer: report of the Advanced Prostate Cancer Consensus Conference 2019. *Eur Urol* 2020; **77:** 508–47.

2 Sartor O, de Bono J, Chi KN, et al. Lutetium-177–PSMA-617 for metastatic castration-resistant prostate cancer. *N Engl J Med* 2021; **385:** 1091–103.

3 Pritchard CC, Mateo J, Walsh MF, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. *N Engl J Med* 2016; **375:** 443–53.

4 Tukachinsky H, Madison RW, Chung JH, et al. Genomic analysis of circulating tumor DNA in 3,334 patients with advanced prostate cancer identifies targetable BRCA alterations and AR resistance mechanisms. *Clin Cancer Res* 2021; **27:** 3094–105.

5 Robinson D, Van Allen EM, Wu YM, et al. Integrative clinical genomics of advanced prostate cancer. *Cell* 2015; **161:** 1215–28.

6 Schiewer MJ, Knudsen KE. DNA damage response in prostate cancer. *Cold Spring Harb Perspect Med* 2019; **9:** a030486.

7 Warner EW, Yip SM, Chi KN, Wyatt AW. DNA repair defects in prostate cancer: impact for screening, prognostication and treatment. *BJU Int* 2019; **123:** 769–76.

8 Ratta R, Guida A, Scotté F, et al. PARP inhibitors as a new therapeutic option in metastatic prostate cancer: a systematic review. *Prostate Cancer Prostatic Dis* 2020; **23:** 549–60.

9 de Bono JS, Mehra N, Scagliotti GV, et al. Talazoparib monotherapy in metastatic castration-resistant prostate cancer with DNA repair alterations (TALAPRO-1): an open-label, phase 2 trial. *Lancet Oncol* 2021; **22:** 1250–64.

10 de Bono J, Mateo J, Fizazi K, et al. Olaparib for metastatic castration-resistant prostate cancer. *N Engl J Med* 2020; **382:** 2091–102.

11 Hussain M, Mateo J, Fizazi K, et al. Survival with olaparib in metastatic castration-resistant prostate cancer. *N Engl J Med* 2020; **383:** 2345–57.

12 Abida W, Campbell D, Patnaik A, et al. Non-BRCA DNA damage repair gene alterations and response to the PARP inhibitor rucaparib in metastatic castration-resistant prostate cancer: analysis from the phase II TRITON2 study. *Clin Cancer Res* 2020; **26:** 2487–96.

13 Abida W, Patnaik A, Campbell D, et al. Rucaparib in men with metastatic castration-resistant prostate cancer harboring a BRCA1 or BRCA2 gene alteration. *J Clin Oncol* 2020; **38:** 3763–72.

14 AstraZeneca. Lynparza film-coated tablets—summary of product characteristics. 2019. https://www.ema.europa.eu/en/documents/product-information/lynparza-epar-product-information_en.pdf. (accessed Aug 23, 2021).

15 AstraZeneca. LYNPARZA® (olaparib) package insert. Wilmington, DE: AstraZeneca Pharmaceuticals, 2020.

16 Clovis Oncology. RUBRACA® (rucaparib) package insert. Boulder, CO: Clovis Oncology, 2020.

17 Washington CR, Moore KN. PARP inhibitors in the treatment of ovarian cancer: a review. *Curr Opin Obstet Gynecol* 2021; **33:** 1–6.

18 Tesaro. ZEJULA™ (niraparib) package insert. Waltham, MA: Tesaro, 2017.

19 Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45:** 228–47.

20 Scher HI, Morris MJ, Stadler WM, et al. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the prostate cancer clinical trials working group 3. *J Clin Oncol* 2016; **34:** 1402–18.

21 US Food and Drug Administration. Premarket approval (PMA): FoundationOne CDx. 2017. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=p170019 (accessed Aug 23, 2021).

22 Heller G, McCormack R, Kheoh T, et al. Circulating tumor cell number as a response measure of prolonged survival for metastatic castration-resistant prostate cancer: a comparison with prostate-specific antigen across five randomized phase III clinical trials. *J Clin Oncol* 2018; **36:** 572–80.

23 Lorente D, Olmos D, Mateo J, et al. Decline in circulating tumor cell count and treatment outcome in advanced prostate cancer. *Eur Urol* 2016; **70:** 985–92.

24 Simon R. Optimal two-stage designs for phase II clinical trials. *Control Clin Trials* 1989; **10:** 1–10.

25 Halabi S, Lin CY, Kelly WK, et al. Updated prognostic model for predicting overall survival in first-line chemotherapy for patients with metastatic castration-resistant prostate cancer. *J Clin Oncol* 2014; **32:** 671–77.

26 Jones P, Wilcoxen K, Rowley M, Toniatti C. Niraparib: a poly(ADP-ribose) polymerase (PARP) inhibitor for the treatment of tumors with defective homologous recombination. *J Med Chem* 2015; **58:** 3302–14.

27 Jensen K, Konnick EQ, Schweizer MT, et al. Association of clonal hematopoiesis in DNA repair genes with prostate cancer plasma cell-free DNA testing interference. *JAMA Oncol* 2021; **7:** 107–10.

28 Maurice-Dror C, Fonseca N, Herberts C, Fan W, Wyatt AW, Chi KN. Circulating tumor DNA fraction (ctDNA%) to independently predict for clinical outcomes in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). *Proc Am Soc Clin Oncol* 2021; **39** (suppl 15)**:** 5049.

29 Chi KN, Rathkopf DE, Attard G, et al. A phase III randomized, placebo-controlled, double-blind study of niraparib plus abiraterone acetate and prednisone versus abiraterone acetate and prednisone in patients with metastatic prostate cancer (NCT03748641). *Proc Am Soc Clin Oncol* 2020; **38** (suppl 6)**:** TPS257.

30 Rathkopf DE, Chi KN, Olmos D, et al. AMPLITUDE: a study of niraparib in combination with abiraterone acetate plus prednisone (AAP) versus AAP for the treatment of patients with deleterious germline or somatic homologous recombination repair (HRR) gene-altered metastatic castration-sensitive prostate cancer (mCSPC). *Proc Am Soc Clin Oncol* 2021; **39** (suppl 6)**:** TPS176.

tomography

MDPI

Article

Whole-Body [^{18}F]-Fluoride PET SUV Imaging to Monitor Response to Dasatinib Therapy in Castration-Resistant Prostate Cancer Bone Metastases: Secondary Results from ACRIN 6687

Mark Muzi [1,*], Finbarr O'Sullivan [2], Timothy G. Perk [3,4], John P. Muzi [1], David A. Mankoff [5], Robert Jeraj [4], Fenghai Duan [6] and Evan Y. Yu [1]

1 School of Medicine, University of Washington, Seattle, WA 98195, USA; jpmuzi@uw.edu (J.P.M.); evanyu@uw.edu (E.Y.Y.)
2 School of Mathematical Sciences, University College, T12 XF62 Cork, Ireland; f.osullivan@ucc.ie
3 AIQ Solutions, Madison, WI 53717, USA; perk@wisc.edu
4 Department of Medical Physics, University of Wisconsin, Madison, WI 53705, USA; rjeraj@wisc.edu
5 Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA; David.Mankoff@pennmedicine.upenn.edu
6 Department of Biostatistics, Brown University, Providence, RI 02912, USA; fduan@stat.brown.edu
* Correspondence: muzi@uw.edu; Tel.: +1-206-543-3517

Abstract: ACRIN 6687, a multi-center clinical trial evaluating differential response of bone metastases to dasatinib in men with metastatic castration-resistant prostate cancer (mCRPC), used [^{18}F]-fluoride (NaF) PET imaging. We extend previous ACRIN 6687 dynamic imaging results by examining NaF whole-body (WB) static SUV PET scans acquired after dynamic scanning. Eighteen patients underwent WB NaF imaging prior to and 12 weeks into dasatinib treatment. Regional VOI analysis of the most NaF avid bone metastases and an automated whole-body method using Quantitative Total Bone Imaging software (QTBI; AIQ Solutions, Inc., Madison, WI, USA) were used. We assessed differences in tumor and normal bone, between pre- and on-treatment dasatinib, and evaluated parameters in association with PFS and OS. Significant decrease in average SUV_{max} and average SUV_{peak} occurred in response to dasatinib. Univariate and multivariate analysis showed NaF uptake had significant association with PFS. Pharmacodynamic changes with dasatinib in tumor bone can be identified by WB NaF PET in men with mCRPC. WB PET has the benefit of examining the entire body and is less complicated than single FOV dynamic imaging.

Keywords: ACRIN 6687; metastatic castration-resistant prostate cancer (mCRPC); bone metastases; [^{18}F]-Fluoride; PET; dasatinib; progression-free survival (PFS); Quantitative Total Bone Imaging (QTBI)

Citation: Muzi, M.; O'Sullivan, F.; Perk, T.G.; Muzi, J.P.; Mankoff, D.A.; Jeraj, R.; Duan, F.; Yu, E.Y. Whole-Body [^{18}F]-Fluoride PET SUV Imaging to Monitor Response to Dasatinib Therapy in Castration-Resistant Prostate Cancer Bone Metastases: Secondary Results from ACRIN 6687. *Tomography* **2021**, 7, 139–153. https://doi.org/10.3390/tomography7020013

Academic Editor: Brian D. Ross

Received: 19 March 2021
Accepted: 22 April 2021
Published: 25 April 2021

1. Introduction

Approximately 70% of men with advanced prostate cancer harbor osteoblastic bone metastases [1]. Imaging of bone metastases typically relies on bone scintigraphy and anatomic modalities such as CT and MRI. However, these methods measure qualitative changes in bone turnover (bone scan) or bone structure (MRI, CT) but not direct metastatic tumor cell activity. Clinically meaningful prostate cancer treatment response has been difficult to define quantitatively, as there is no uniformly accepted surrogate marker that correlates with long-term outcomes to optimally guide patient management and new drug development.

The use of positron emission tomography (PET) to monitor response to therapy in prostate cancer is inherently quantitative. PET can measure in vivo tumor and normal tissue biology using tracers to map many metabolic pathways, including bone osteoblastic metabolism using [^{18}F]-fluoride (NaF) PET [2,3]. NaF PET offers a quantitative measure of osteoblastic bone formation and remodeling, and is appropriate for imaging the blastic lesions observed in prostate cancer [4]. Additionally, when compared to standard ^{99M}Tc-

based bone scintigraphy, NaF PET offers improved sensitivity of detection and when combined with CT, specificity is also improved [5–7].

ACRIN 6687 was a prospective, multi-center phase 2 trial that used NaF PET to probe the response of dasatinib (SPRYCEL®; Bristol-Myers Squibb) treatment, a SRC kinase inhibitor that decreases bone turnover, in men with metastatic castration-resistant prostate cancer (mCRPC) [8]. The trial was designed to evaluate differential response of normal and tumor bone to dasatinib treatment using NaF PET using a protocol that began with dynamic single field-of-view (FOV) imaging and then was followed by static whole-body (WB) scans with multiple FOVs. Previous kinetic modelling results from single FOV dynamic imaging found significant differences in changes of the PET kinetic parameters from tumor bone compared to normal bone in response to dasatinib treatment. Changes in the 30–60 min summed SUV metrics from the dynamic acquisition had a modest association ($p = 0.056$, $n = 12$ patients) with progression-free survival (PFS), where progression was determined by the Prostate Cancer Working Group 2 (PCWG2) [9] criteria.

Although the initial results for the ACRIN 6687 trial were intriguing, we recognize the potential limitations of dynamic single FOV analyses for general use and widespread adoption. Specifically, although dynamic studies may offer breadth of analysis, the level of complexity and lack of standardization are not practical for broad utilization. In the initial set of analyses using the 30–60 min SUV images, changes in the average SUV_{max} for up to 5 tumors (SUV_{maxavg}) in a patient not only had significant differential changes to dasatinib therapy in tumor vs. normal bone, but those changes had marginal association with progression free survival (PFS); these were features not displayed by dynamic Ki (metabolic flux) or K_1 (tracer transport) kinetic parameters. This lends further credence to the concept of simplifying the NaF PET image analysis with SUV only. Additionally, the previously reported limited FOV may have omitted important information from metastatic lesions outside of the single FOV. As part of a post-hoc analysis not proposed in the original ACRIN 6687 clinical trial, we sought to determine if important information obtained from outside of the dynamic FOV could offer additional clinical and prognostic information, comparable and/or incremental to earlier published dynamic data. Previous reports using WB fluoride analysis also showed a relationship of SUV measures to PFS for patients that received either a docetaxel-based chemotherapy regimen or an androgen receptor pathway inhibitor [10]. Here we examine SUV analysis results from multi-FOV WB static NaF PET imaging scans, acquired after a one-hour dynamic scan, in mCRPC patients recruited to ACRIN 6687 at baseline and after receiving 12 weeks of dasatinib treatment. Statistical analysis of the clinical and PET imaging data was undertaken in order to identify potentially interesting associations between various biomarkers (PET and blood borne) and patient outcomes. As is the nature of secondary investigations, the reported data analysis and relationships cannot be interpreted in the same way that the analysis for the primary hypothesis of the underlying clinical trial that has been reported [8].

2. Materials and Methods

2.1. Study Design

Study design and treatments (Supplementary Materials, Figure S1), patient eligibility, imaging protocol, regulatory approval, radiochemistry and study endpoints have been previously described [8]. Briefly, American College of Radiology Imaging Network (ACRIN) 6687 was a phase 2 trial conducted by ACRIN at 4 Prostate Cancer Clinical Trials Consortium (PCCTC) centers: University of Washington, Duke University, Oregon Health Sciences University and the Dana-Farber Cancer Institute (NCT00936975). ACRIN 6687 protocol was approved at each site's institutional review board and other local regulatory agencies. Informed consent was obtained from all individual participants included in the study prior to trial enrollment. Patients enrolled on the study had to have metastatic castration-resistant prostate cancer with at least one convincing bone metastasis defined by bone scintigraphy, CT scan or plain X-ray. All patients eligible for ACRIN 6687 were first enrolled in a clinical trial (NCT00918385) where patients were selected either for nilutamide or dasatinib based

on a 300-gene signature found on a metastatic biopsy. Only patients receiving dasatinib were imaged on ACRIN 6687. The PET imaging protocol included a single field-of-view (FOV) low-dose CT scan for attenuation correction, a one-hour dynamic PET emission scan consisting of 45 time frames over 60 min immediately following the NaF injection, a multiple FOV (range 5–7 FOV) WB PET emission scan from base of skull to mid-thigh and a multiple FOV WB low-dose CT scan. Eligible patients with bone mCRPC underwent the WB NaF PET scan, that occurred starting at approximately 75 min (range 53 to 95 min) after NaF injection, with an on-average mid scan time of 90 min (range 64–110 min) prior to and 12 weeks after the onset of treatment with dasatinib therapy to determine if the nature of the drug effect could be ascertained through PET/CT imaging. The WB scans were approximately 25–40 min in duration, making the uptake time range from the start to the end of the scan 53–130 min after injection with a mean mid scan time of 90 min. Individual patient WB PET scan acquisition parameters and reconstructed image resolution values appear in Supplementary Materials Table S1 and the WB time profile in Figure S2. Additional scanning before and while on dasatinib treatment included a clinical CT scan and a ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP) bone scan.

2.2. Clinical Assessments

Patients were clinically followed after initiation of dasatinib with clinical visits every 4 weeks and repeated bone and CT scan imaging every 12 weeks until radiographic or clinical progression, significant toxicity necessitating cessation of dasatinib or until patient withdrawal from the trial. Baseline pathologic Gleason grade scores from archival prostate tissue was obtained from local participating sites. Biomarkers from blood and urine samples obtained at baseline and throughout therapy included bone alkaline phosphatase (BAP), an indicator of bone metabolism, urine N-telopeptide (uNTX), an indicator of bone resorption and prostate specific antigen (PSA), an indicator of progressive disease.

2.3. PET Image Analysis

Unlike the previous single dynamic FOV investigation surrounding the pelvis and lower spinal column, WB image analysis used both a traditional lesion-level volume-of-interest (VOI) method and a whole-body patient-level assessment. The lesion-level VOI method collected up to 5 of the most NaF avid bone metastases using the highest NaF SUV_{max} uptake value, the maximal voxel within a 1cc VOI, on the baseline scan. The average activity from a 1cc spherical VOI placed over the hottest region of the tumor as described in the PERCIST protocol [11] was the SUV_{peak}. These VOIs were placed in the same anatomical location on the mid-therapy scan. Based on previous reports, only tumors with a SUV_{peak} threshold of 15 g/mL were included in the analysis [10,12]. Although Kurdziel et al. used a segmentation SUV threshold of 10 g/mL [13], a later study by Rohren et al. showed that lesion ROIs identified using this threshold still included normal bone activity [14]. Lesions smaller than 1.5 cc as measured by PET volume were also excluded.

Each selected tumor region from the NaF PET and corresponding CT images was reviewed by an experienced PET image nuclear medicine radiologist and a prostate cancer oncologist and confirmed as malignant. Bone lesion VOIs, along with matched areas of normal bone, were used for intensity analysis by SUV_{max} and SUV_{peak}. Tumor assessments were performed using the average of up to 5 tumors from each patient, using the notation from the original ACRIN 6687 report of SUV_{maxavg} and $SUV_{peakavg}$ and the index lesion SUV_{max} for each patient. The index lesion was the single lesion with the most NaF avidity. These SUV metrics have been shown to be useful in prior studies of NaF PET imaging of mCRPC patients for evaluation of treatment response [8,10,15,16]. Tumor-matched normal bone regions identified by both CT and NaF PET of identical volume to tumor regions were also constructed.

2.4. Quantitative Total Bone Imaging (QTBI) Analysis

Whole-body patient-level image analysis utilized the bone metastases software application from the University of Wisconsin and AIQ Solutions (Madison, WI, USA) [12,17]. Briefly, CT images were segmented into skeletal regions using an atlas-based segmentation approach [18], then region-specific optimized thresholds were used to detect lesions [19] on the PET image. Following lesion detection, a random forest model and manual review were applied to exclude lesions that were likely to be benign [20]. Patient-level PET parameters used for tumor assessment included $qSUV_{max}$, $qSUV_{peak}$, $qSUV_{total}$ (total tumor burden) and qVF (volume fraction), where the q indicates that the parameters are derived from QTBI analysis. The peak SUV was determined by placing 1cc spheres on each of the 5 lesions with the highest SUV_{max} and averaging the extracted values.

2.5. Statistics

Pre- and on-treatment differences of lesion-level and patient-level PET parameters were assessed using standard paired t-tests. Repeatability studies showed that SUV_{max} from lesion level analysis coefficient of variation was 14.1%, while at the patient level, it was slightly smaller: 12.0% [12]. Variation of other PET SUV metrics from repeatability analysis were similar in magnitude. While the data have limited power to properly verify normality of the underlying data, the Shapiro-test of normality showed little evidence of departure from such an assumption. *p*-values obtained by the t-test were found to be in close agreement with those obtained using a non-parametric Wilcox rank test approach. Pairwise comparisons were summarized in terms of rank correlations. Rank correlation was used because it has the ability to evaluate monotone relations, not just linear ones. Note that overall, 96 separate *p*-values were generated in this analysis. It is important to appreciate that the *p*-values reported are without adjustment for multiple comparisons. Our justification for this is that results presented are not offered as definitive resolutions to the 96 hypotheses being considered, instead they are presented as a way to guide the selection of a much more limited set of hypotheses that might merit further investigation in a prospective clinical trial. See the discussion for further comment.

Pre-treatment PET values and the change from pre- to on-treatment PET values were evaluated in association with PFS and overall survival (OS), both of which are continuous variables measured in days from the onset of dasatinib treatment. PFS is determined as the number of days from dasatinib treatment to the first progression event as evaluated by PCWG2 criteria. The relationship between PET parameters and outcome measures of PFS was evaluated by univariate and multivariate regression analysis. The overall survival (OS) data are incomplete (censored) and so a Cox proportional hazards model was used for both univariate and multivariate analysis.

For multivariate regressions, we report *p*-values associated with the PET parameter combined with the base model. This approach assesses the additional prognostic contribution of the PET parameter, after adjustment for a base model of established clinical variables; age and baseline ln(BAP). The *p*-values reported for the SUV variables in multivariate analysis assess the added impact of the SUV variables in a context where there is adjustment (by the multivariate method) for the ln(BAP) and age covariates. These are not *p*-values for the overall model. The multivariate analysis gives a more precise appreciation of the 'added-benefit' of the PET information. In the case of OS, the effects of the PET variables are reported in terms of the excess risk, or hazard ratio (HR), associated with a 1-SD change in the PET variable.

As a result that the PFS data were complete (no censoring), the relation between prognostic factors, such as age, BAP or PET variables, and PFS was analyzed by multiple linear regression. Cox modeling analysis was also considered, but given the more precise nature of regression analysis, the multiple regression analysis was used in this report. Given the limited sample size and the consequent concerns regarding the adequacy of standard asymptotic Gaussian approximations for inferences, Efron's Bootstrap [21] with 500 replicates was used in multivariate outcome analysis.

Effects were assessed using a two-sided z-test based on the bootstrap estimated mean and standard error (SE) values. Additionally, changes in PET uptake parameters in response to dasatinib treatment, were compared with changes in markers of bone turnover, urinary N-telopeptide (uNTX), bone alkaline phosphatase (BAP) and PSA using Kendall's tau-b correlation. All statistical tests were performed in R, and acronyms are defined in Table 1.

Table 1. Definition of acronyms.

Acronym	Definition
Δ	The difference of a parameter between scan 2 and scan 1
^{99m}Tc-MDP	^{99m}Tc-methylene diphosphonate
ACRIN	American College of Radiology Imaging Network
AR	Androgen receptor
BAP	Bone alkaline phosphatase
CT	Computed tomography
Diff	The difference of a parameter between scan 2 and scan 1
FOV	Field of view, usually axial
HR	Hazard ratio
index SUV_{max}	The hottest baseline lesion (index lesion) SUV_{max} value
index SUV_{peak}	The hottest baseline lesion (index lesion) SUV_{peak} value
K1	A model parameter estimating transport of the tracer from blood to tissue
Ki	Metabolic flux determined from the model parameters $(K_1 \times k_3)/(k_2 + k_3)$
mCRPC	Metastatic castration resistant prostate cancer
MIP	Maximal image projection flattening a 3D image series to 2D
MRI	Magnetic resonance imaging
NaF	^{18}F-sodium fluoride
OS	Overall survival
PCWG2	Prostate cancer working group 2
PET	Positron emission tomography
PFS	Progression free survival
Pval	The *p*-value of a comparison between two arrays of data
$qSUV_{max}$	QTBI analysis of SUV_{max}, the maximum uptake in the tumor volume (g/mL)
$qSUV_{peak}$	QTBI analysis of SUV_{peak} (g/mL)
$qSUV_{total}$	QTBI analysis of total tumor burden, the sum of voxel SUVs in the tumor volume.
QTBI	Quantitative total bone imaging analysis software, AIQ Solutions, Madison, WI
qVF	QTBI analysis of the tumor volume fraction compared to the total bone volume
ROI	Region of interest
SE	Standard Error
SUV	Standard uptake value
SUV_{max}	The maximum SUV voxel within a tumor (g/mL)
SUV_{maxavg}	The average of up to 5 tumor SUV_{max} values (g/mL)
SUV_{peak}	The average activity of a 1cc spherical VOI over maximal tumor activity (g/mL)
$SUV_{peakavg}$	The average of up to 5 tumor SUV_{peak} values (g/mL)
uNTX	Urinary N-telopeptide
VOI	Volume of interest
WB	Whole-body PET scan

3. Results

3.1. Patients

Of the 18 patients enrolled in the trial (median age 69 years range 48–86), one withdrew from the study with no follow-up on PFS or OS after the first PET scan, and was excluded from this analysis leaving 17 evaluable patients for WB PET baseline imaging. Three patients, with worse baseline prognostic features, did not undergo an on-treatment PET imaging study due to clinical progression while on dasatinib; this resulted in early discontinuation from the trial prior to the second imaging time point. In our initial ACRIN 6687 publication on dynamic imaging results, two studies were omitted due to technical issues with the dynamic scan, but their WB scan was useable for this analysis and therefore were included. Seventeen patients had either met progression criteria or death by the

time of this investigation. Thus, 14 patients had evaluable pre- and on-treatment dasatinib WB NaF PET imaging. The baseline patient and PET imaging characteristics appear in Supplemental Materials Table S1.

3.2. PET Findings

In the original single FOV report for ACRIN 6687 [8], up to 5 bone lesions were selected by the local site physician, which occurred in the pelvis or along the lower spinal column. The WB tumor selection criteria at the lesion level presented in this report was determined by averaging up to 5 of the highest NaF SUV_{max} uptake bone lesions using a lower threshold of 15 g/mL. However, only 19 WB regions of the 70 dynamic regions (27%) overlapped between the dynamic and static PET series (Figure 1). Thus, many of the hottest lesions from the WB SUV images acquired at an average mid-acquisition time of 90 min after injection were not present in the single FOV SUV image acquired precisely at 45 min (30–60 min summed SUV) from the dynamic series. A summary of the lesion-level PET parameter values before and while on-dasatinib treatment appear in Table 2. Individual patient NaF PET SUV uptake values appear in Supplementary Materials Table S2. The average uptake values for all tumors from a patient study were represented as $SUV_{peakavg}$ and SUV_{maxavg}, while the values for the hottest single index lesion from each patient were represented as index SUV_{max} and index SUV_{peak}. Fifteen of the 17 evaluable patients had 5 tumor sites above the threshold, while 1 patient had 2 tumor sites and 1 patient had 1 tumor site above the SUV_{peak} threshold of 15 g/mL. Significant average decreases were observed in SUV_{maxavg} (−20% ± 12% 95%CI, $p = 0.001$), $SUV_{peakavg}$ (−17% ± 14% 95%CI, $p = 0.013$), index SUV_{max} (−16% ± 14% 95%CI, $p = 0.025$) and index SUV_{peak} (−16% ± 15% 95%CI, $p = 0.049$) in bone metastases in response to dasatinib, while no significant change was observed in normal bone (Figure 2). Significance was based on repeatability results of NaF in mCRPC patients [12]. Significant differences in changes from tumor bone compared to normal bone in response to dasatinib were noted for SUV_{maxavg} ($p = 0.004$) and $SUV_{peakavg}$ ($p = 0.028$).

Table 2. [^{18}F]-Fluoride uptake parameters in bone tumors.

Parameters	Baseline NaF PET (SD)	On-Dasatinib NaF PET (SD)	Change On-Dasatinib (SD)	% Change (*p*-Value)
† Lesion-level				
SUV_{maxavg} (g/mL)	47.1	38.3	−9.5	−20.1%
	(16.7)	(17.0)	(9.6)	**(0.001)**
$SUV_{peakavg}$ (g/mL)	34.5	28.8	−5.8	−16.2%
	(13.3)	(13.0)	(8.3)	**(0.013)**
Index SUV_{max} (g/mL)	60.0	52.8	−9.8	−14.3%
	(27.3)	(24.9)	(14.7)	**(0.025)**
Index SUV_{peak} (g/mL)	45.8	40.3	−7.1	−12.9%
	(21.6)	(18.8)	(11.3)	**(0.049)**
‡ Patient-Level				
$qSUV_{max}$ (g/mL)	61.2	64.5	−2.7	0.3%
	(27.4)	(26.1)	(13.9)	(0.569)
$qSUV_{peak}$ (g/mL)	37.6	37.8	−0.6	2.2%
	(15.7)	(12.5)	(7.0)	(0.470)
$qSUV_{total}$ (g/mL × cc)	8234	7307	576	30.0%
	(8914)	(6950)	(1553)	(0.176)
qVF	9.9	8.8	0.3	25.8%
	(10.2)	(8.3)	(0.5)	(0.120)

† Lesion-level average results and average change for 17 patient values at baseline and 14 patients that were scanned while on-dasatinib with standard deviation below in parentheses. Lesion-level Index is the single hottest lesion for the patient. ‡ Patent-level parameters from QTBI analysis, indicated by a q preceding the parameter, was performed on 16 patients at baseline and 12 while on-dasatinib. Patient-level qVF is the volume fraction of the tumor from QTBI analysis. Boldface type indicates a significant ($p \leq 0.05$) decrease in the PET value from baseline.

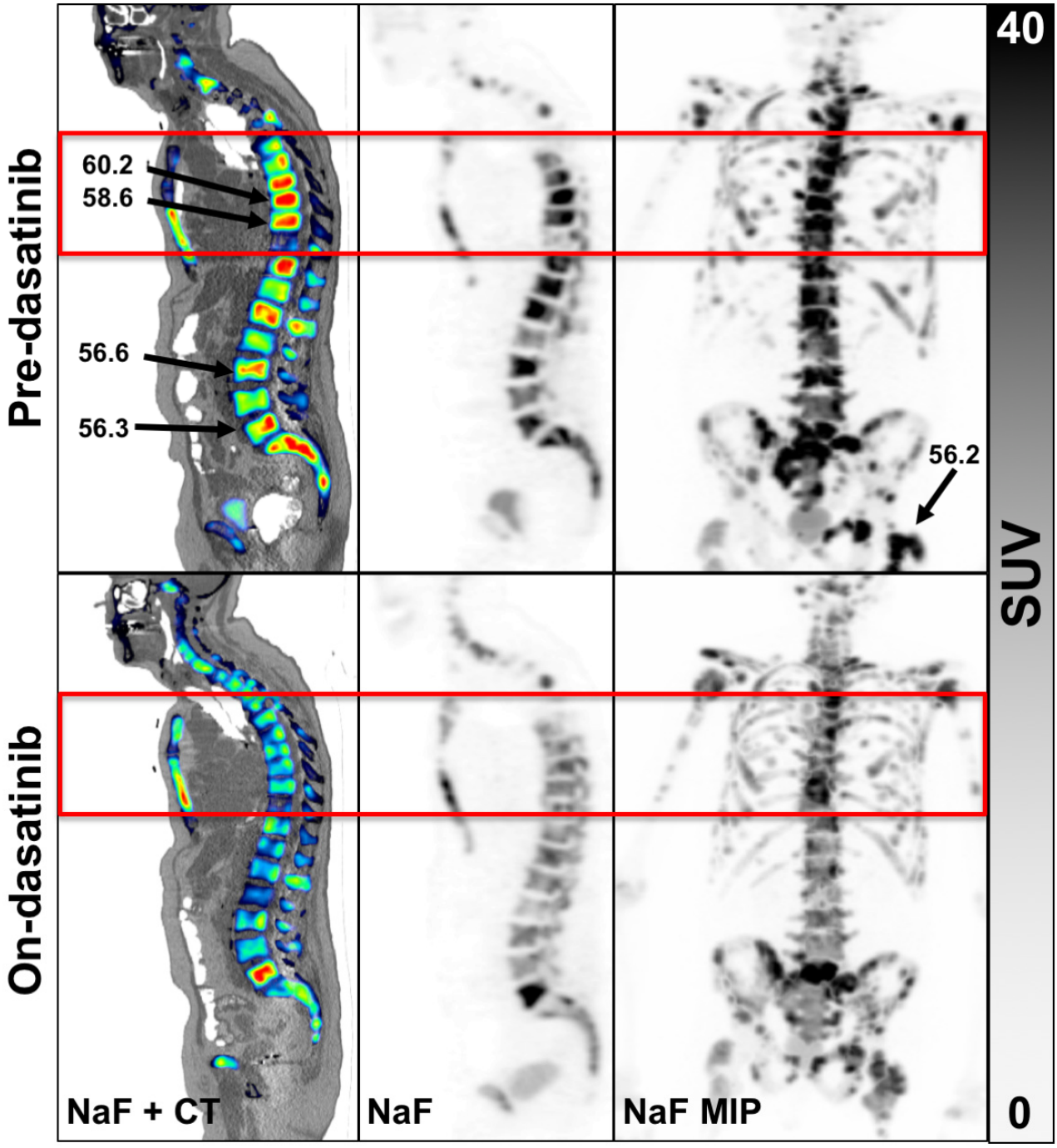


Figure 1. Example of an 82-year-old patient scan 1 (**top** row) and scan 2 (**bottom** row). Panels left to right, NaF overlaid on CT, NaF alone and with NaF PET maximal image projection (MIP) of the entire WB volume. The red box is the single FOV for the dynamic scan. Three of the 5 hottest tumors were not located in the single dynamic FOV, the results of which were reported previously [8]. An example WB patient with none of the hottest tumors in the dynamic FOV appears in Supplementary Materials Figure S3.

Results of patient-level QTBI analysis used only 15 patient scans at baseline and 12 s time point on-treatment scans due to technical issues related to image scaling and image quality for 2 patients between the dual time point scans. No significant change between pre-dasatinib and on-treatment NaF uptake for $qSUV_{max}$, $qSUV_{peak}$, $qSUV_{total}$ and VF was observed for the 12 patients (Table 1). Individual patient-level QTBI uptake values appear

in Supplementary Materials Table S3 with a patient example analysis in Supplementary Materials Figure S4.

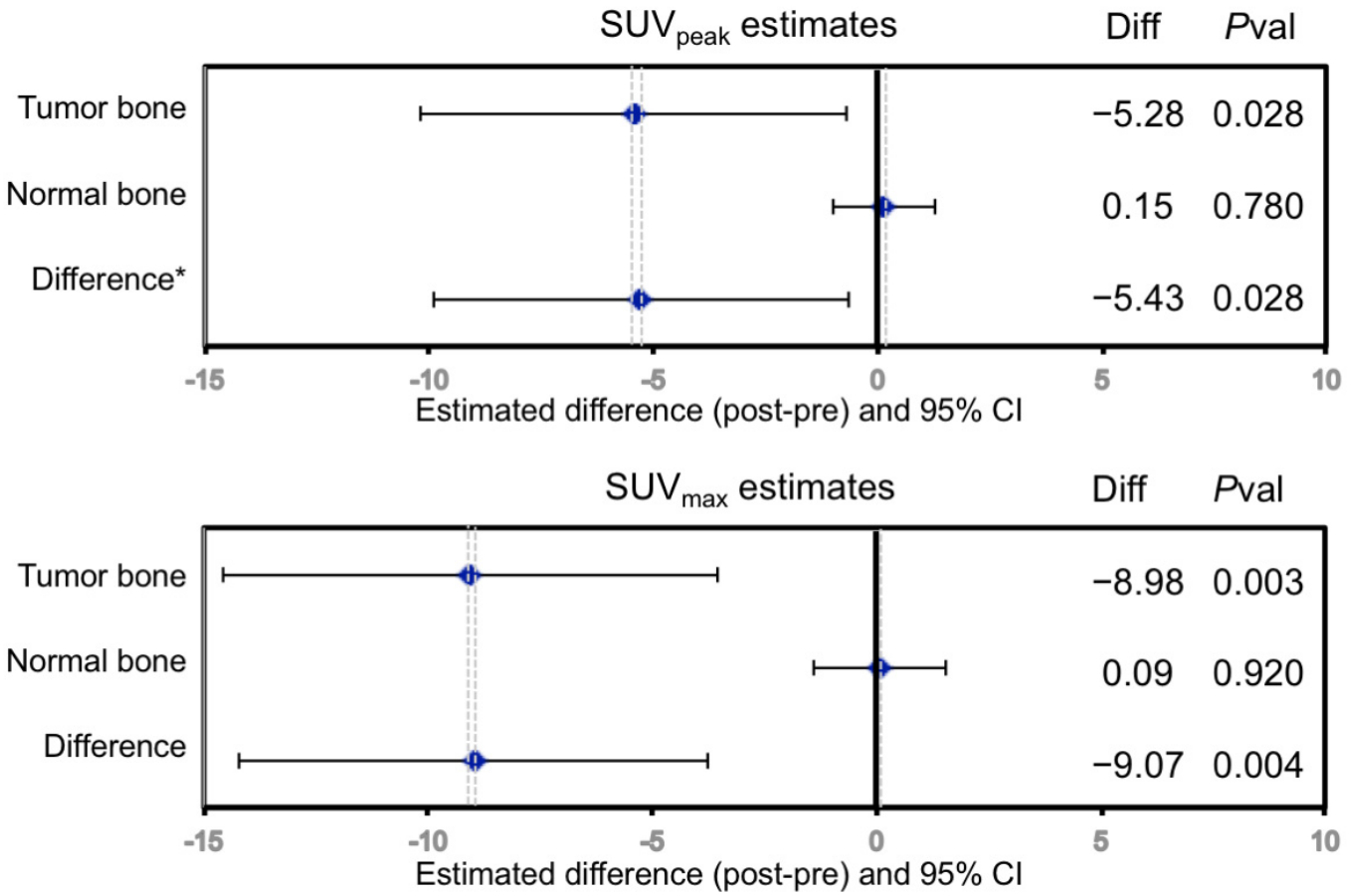


Figure 2. Change in regional ^{18}F uptake in response to dasatinib treatment in mCRPC bone metastases measured by SUVpeak, SUVmax. No significant changes were seen in normal bone. Diff = Scan2—Scan1; *P*val = *p*-value. * Difference = Δ in tumor bone—Δ in normal bone.

3.3. Statistical Analyses

In the case of progression, the data are complete (no censoring) so standard multiple linear regression analysis was used. However, for OS, 3 patients were censored of the 17 evaluable patients and a Cox proportional hazard model was applied to account for censoring.

In univariate analysis of PET variables as predictors of PFS (Table 3), only elevated baseline $qSUV_{total}$ and baseline qVF were significantly associated with PFS ($p = 0.023$ and $p = 0.011$, respectively), where higher values lead to earlier progression. There was no clear association of the change in any other lesion-level or patient-level PET parameter with PFS or OS for univariate analysis unlike the univariate analysis results of the original ACRIN 6687 report that showed a borderline correlation of change in SUV_{maxavg} to PFS ($p = 0.056$). Bootstrap results are not reported for univariate analyses, but they are provided in Supplementary Materials Table S4.

In multivariate analyses (Table 4), the regression model included age, the logarithm of baseline bone alkaline phosphatase (ln(BAP)) and the PET parameter as covariates. Age and ln(BAP) were found to be strong predictors of disease progression in univariate analysis [8]. Baseline lesion-level SUV_{maxavg} and $SUV_{peakavg}$ values from the 17 patients showed an association with PCWG2 PFS ($p = 0.043$ and $p = 0.018$, respectively) using multivariate analysis. The multivariate analysis used for QTBI parameters had the same

base model of age and ln(BAP) described above, and showed that baseline $qSUV_{peak}$ also had a significant relationship with PFS ($p = 0.025$). The multivariate analysis showed no relationships to OS for any PET parameter at baseline or change in the parameter while on-dasatinib. The original report for ACRIN 6687 [8] did not perform multivariate analysis.

Table 3. Univariate analysis of PET variables to PFS and OS (*p*-values, HR).

PET Parameter	PFS	OS	HR
† Lesion-Level			
$SUV_{maxavg}1$	0.549	0.547	1.199
ΔSUV_{maxavg}	0.836	0.253	0.659
$SUV_{peakavg}1$	0.437	0.494	1.229
$\Delta SUV_{peakavg}$	0.622	0.443	0.765
Index $SUV_{max}1$	0.631	0.726	1.112
Index ΔSUV_{max}	0.760	0.407	0.739
Index $SUV_{peak}1$	0.630	0.678	1.128
Index ΔSUV_{peak}	0.884	0.336	0.716
‡ Patient-Level			
$qSUV_{max}1$	0.850	0.745	1.101
$\Delta qSUV_{max}$	0.780	0.634	0.848
$qSUV_{peak}1$	0.553	0.454	1.285
$\Delta qSUV_{peak}$	0.781	0.485	0.787
$qSUV_{total}1$	**0.023**	0.061	1.884
$\Delta qSUV_{total}$	0.889	0.260	0.668
qVF1	**0.011**	0.104	1.687
ΔqVF	0.680	0.704	0.869

† The lesion-level analyses were performed on up to 5 tumors per patient selected by uptake intensity for 17 patients at baseline. The change (Δ) while on-dastinib was determined on 14 of the 17 patients. The PFS column has the *p*-value for the PET parameter in analysis of PCWG2 progression free survival. The OS column has the *p*-value for the PET parameter in the analysis of overall survival, and HR has the associated hazard ratio corresponding to a 1-SD increase in the PET parameter. ‡ The patient-level whole-body QTBI analyses were performed on 16 patients at baseline, while change was determined on 12 of the 16 patients. Boldface type indicates a significant ($p \leq 0.05$) association with outcome.

Table 4. Multivariate analysis of PET variables to PFS and OS (*p*-values, HR).

† PET Parameter	PFS			OS		
	Days	SE	*p*-Value	HR	SE	*p*-Value
Lesion-Level						
$SUV_{maxavg}1$	26.5	13.1	**0.043**	1.135	0.856	0.875
ΔSUV_{maxavg}	−2.1	21.5	0.923	0.800	1.081	0.853
$SUV_{peakavg}1$	32.0	13.5	**0.018**	1.421	2.770	0.879
$\Delta SUV_{peakavg}$	−10.4	21.9	0.635	1.142	3.486	0.968
Index $SUV_{max}1$	17.3	14.2	0.222	1.296	2.552	0.908
Index ΔSUV_{max}	0.7	18.3	0.971	1.196	4.299	0.964
Index $SUV_{peak}1$	21.5	15.4	0.163	1.443	3.250	0.892
Index ΔSUV_{peak}	−2.4	17.4	0.888	0.874	0.874	0.885
Patient-Level						
$qSUV_{max}1$	17.6	19.2	0.359	1.321	2.759	0.908
$\Delta qSUV_{max}$	0.9	27.2	0.972	1.341	4.186	0.935
$qSUV_{peak}1$	36.9	18.3	**0.044**	1.646	3.191	0.840
$\Delta qSUV_{peak}$	−15.4	18.8	0.413	1.003	1.609	0.999
$qSUV_{total}1$	0.7	20.9	0.972	2.911	6.061	0.753
$\Delta qSUV_{total}$	14.1	25.4	0.580	0.635	1.396	0.794
qVF1	−11.2	21.6	0.606	1.977	4.017	0.808
ΔqVF	15.7	21.2	0.458	0.708	1.063	0.783

† The multivariate model used age, ln(BAP) and the PET parameter. For association with PFS multiple linear regression was used as the data were not censored. PFS days are the number of days corresponding to a 1-SD increase in the PET parameter, and SE is the standard error of Days. Cox proportional hazard modeling was used to determine association of the multivariate model to OS, where 4 patients were censored. The hazard ratio (HR) is the associated hazard ratio corresponding to a 1-SD increase in the PET parameter. The lesion-level analyses were performed on 17 patients at baseline (indicated by 1 after the parameter), while change on-dasatinib was determined on 14 of the 17 patients. The patient-level whole-body QTBI analyses were performed on 16 patients at baseline, while change was determined on 12 of the 16 patients. Boldface type indicates a significant ($p \leq 0.05$) association with outcome.

The actual PFS versus the predicted progression based on multivariate regression analysis is shown in Supplementary Materials Figure S5. The predicted progression relies on the multivariate base model that includes the covariates of age and baseline ln(BAP) with the addition of a PET parameter and shows a high correlation (r = 0.83) between the actual and predicted progression (p = 0.001).

Changes in patient and lesion-level NaF PET uptake parameters in response to dasatinib in bone metastases to the change in PSA and bone biomarkers appear in Table 5. Specifically, change in BAP had a significant negative correlation with baseline NaF PET assessed by lesion-level $SUV_{peakavg}$ and SUV_{maxavg}. Universally, PET uptake parameters decreased from before to while on-dasatinib treatment, while BAP levels increased or stayed the same. Change in uNTX was correlated to the SUV_{max} of the index lesion, but no other PET variables. PSA had no correlation with changes in any NaF PET uptake values.

Table 5. Correlations between change of NaF PET parameters and change in biomarkers.

† PET Parameter	ΔuNTX	ΔBAP	ΔPSA
ΔSUV_{maxavg}	0.31 (0.142)	**−0.41** **(0.047)**	0.08 (0.747)
$\Delta SUV_{peakavg}$	0.26 (0.221)	**−0.45** **(0.026)**	0.12 (0.591)
ΔIndex SUV_{max}	0.44 **(0.037)**	−0.21 (0.331)	0.14 (0.518
$\Delta IndexSUV_{peak}$	0.23 (0.270)	−0.36 (0.080)	−0.01 (1.00)
$\Delta qSUV_{max}$	0.11 (0.630)	0.00 (1.000)	0.15 (0.545)
$\Delta qSUV_{peak}$	0.02 (0.945)	−0.27 (0.250)	0.12 (0.638)
$\Delta qSUV_{total}$	−0.17 (0.450)	0.03 (0.947)	0.42 (0.063)
ΔqVF	0.17 (0.450)	−0.06 (0.841)	0.39 (0.086)

† Kendall tau β rank correlation values (and p-values) between the change of NaF PET parameters and the change in PSA and bone biomarkers. Significant correlation of p-values ($p \leq 0.05$) appear in boldface type.

4. Discussion

Similar to the results in our previous report of ACRIN 6687 evaluating a limited dynamic FOV, NaF PET WB uptake also reveals the distinct patterns of pharmacodynamic changes in bone mCRPC from normal bone in response to therapy with dasatinib, as displayed in Figure 2. There appears to be a differential effect of dasatinib on normal compared to tumor bone in men with mCRPC, as measured by fluoride uptake and fluoride bone incorporation.

The previous ACRIN 6687 report [8] showed that SUV_{maxavg} from a single FOV NaF image summed exactly from 30–60 min had a large decrease in bone mCRPC uptake in response to treatment with dasatinib, and that a decrease in SUV_{maxavg} marginally correlated with shorter PFS (p = 0.056), indicating that patients with a lower decline in SUV_{maxavg} had longer PFS. In the current WB lesion-level SUV analysis, baseline or changes in uptake measures collected later, on average WB imaging starting approximately 75 min after injection (range 53 to 95 min), failed to find significance with PFS or OS in univariate analysis. The later WB scan acquired with a mid-scan average of 90 min after injection (range 65 to 110 min) might be different from the single FOV dynamic scan collected precisely at mid-scan 45 min (30 to 60 min SUV image) due to tracer clearance that is independent of the disease, fewer counts with increased noise and the large variability of uptake time between patient WB scans, that all have the effect of increasing variability.

The wide range in the time of WB image acquisition from the injection time in this multi-center trial can increase variability in SUV measurements by as much as 25% for 15 min deviations [22,23] and may significantly affect the correlation of WB NaF measures to PFS where uptake times differ by more than 40 min.

The assessment of up to the 5 hottest tumors with a threshold SUV, is similar to prior methods, but may not be as useful as the selection of tumors and imaging FOV by local clinicians that utilized information based on their clinical impression of the patients in the ACRIN 6687 primary aim report [8]. Averaging the SUV_{peak} or SUV_{max} over 5 tumors may capture the intensity, but not the spatial distribution of a tumor and [10,15] therefore may be unable to determine total tumor burden, as the QTBI analysis offers. Using QTBI analysis, Harmon et al. [10] have found that total tumor burden determining a SUV_{total} metric via bone segmentation followed by thresholding the NaF SUV at 15g/mL has been valuable in assessing response in mCRPC patients using an effective therapy, such as androgen receptor pathway inhibitors or a docetaxel-based chemotherapy regimen. Patient-level WB assessment using QTBI software for the patients presented here did show that large baseline total tumor burden ($qSUV_{total}$) and tumor volume fraction (qVF) were significantly associated with shorter PFS in univariate analysis, suggesting that a large, intense tumor burden at baseline indicates poor clinical outcome. However, in univariate analysis the change in patient-level PET parameters from QTBI analysis failed to show a relationship to PFS, and no patient-level parameter showed association with OS.

The inability to observe a definitive relationship between changes in NaF PET uptake and PFS or OS may also be because the effect of dasatinib in mCRPC patients is marginal. Dasatinib has not been successful in demonstrating overall survival benefit in phase 3 trials of men with mCRPC [24]. Although the effects of dasatinib on bone have been clearly documented, it does not appear to offer significant anti-tumor efficacy [25,26]. The lack of association of changes in PET parameters to PFS or OS may be that the disease burden was so high in these mCRPC patients, that any response was buried in either PET measurement variability or dasatinib is an ineffective antineoplastic treatment against mCRPC.

However, a multiple variable statistical model that has covariates of age, a clinical biomarker (baseline ln(BAP)) and an NaF PET uptake measure showed that lesion-level baseline SUV_{maxavg}, baseline $SUV_{peakavg}$ and patient-level baseline $qSUV_{peak}$ were all significantly associated with longer PFS in this small cohort (Table 4). No PET parameter used in multivariate modeling analysis showed significant association with OS. The major multivariate model driving component is ln(BAP), which along with age and measures of NaF uptake aids in optimizing the estimates of progression. BAP and NaF uptake are expected to be closely related, as bone turnover (BAP) goes hand-in-hand with new bone formation and matrix mineralization (fluoride uptake on NaF PET). High baseline BAP and high NaF uptake might indicate a more favorable blastic phenotype and longer progression, while baseline BAP and lower NaF might indicate a more lytic phenotype and more aggressive clinical behavior.

The statistical results for the multivariate analysis might be affected by the large variation in image acquisition times between patients (see Supplementary Materials Figure S2), which can increase variability by as much as 75% for over 40 min deviation in uptake time between patient scans [22,23]. Outcomes using NaF PET have been different when more efficacious agents, with proven survival benefit, such as androgen axis inhibiting therapeutics or docetaxel chemotherapy have been used. In prior published studies with a larger cohort of patients (n = 56), mid-treatment findings with NaF imaging alone have association with PFS [10]. This suggests that NaF PET imaging has potential for assessment of treatment efficacy of some therapies in men with mCRPC.

Interestingly, we observed a negative correlation between a decreasing change in lesion-level SUV parameters (ΔSUV_{maxavg}, $\Delta SUV_{peakavg}$, ΔIndex SUV_{max}) and an increase in bone alkaline phosphatase (ΔBAP). This relationship was noted in the initial report on the ACRIN 6687 trial that patients with the largest decrease in PET uptake parameters had worse outcome than those that stayed the same or increased [8]. An increase in BAP

levels may be due to dasatinib treatment, which has been shown previously to promote osteoblast differentiation [27] and mineralization that could lead to a relative activation and a transient increase in BAP levels indicative of a healing or reparative response [28–30]. Increased osteoblastic activity would also be expected to lead to a relative increase of NaF uptake. We did not follow these patients after completion of dasatinib treatment with repeat measurements of BAP, thus it is speculative to associate a decrease in BAP levels in this small cohort of patients with better outcome; however, this finding indicates some mechanistic consistency between prior findings based on dynamic imaging and the current WB analysis. Change in uNTX and PSA had no correlation with changes by NaF PET.

Given the very limited capacity of the dataset (n = 17 at baseline, n = 14 with an additional scan at 12 weeks into therapy) and the many measurements carried out, there is no real scope to carry out any type of internal cross-validation. The bootstrapping approach used in evaluating the relationship between PET variables and outcomes (PFS and OS) provides more defensible estimates of statistical significance of the reported effects and provides some measure of adjustment for the limited sample size. Nevertheless, our exploratory analysis is mainly offered to provide some guidance on what relationships may be worth future investigation via a prospective clinical trial. The most glaring limitation of this study, however, was the small number of evaluable patients recruited and an even smaller subset that completed the second PET scan during dasatinib treatment, limiting statistical power for prediction of PFS and OS.

5. Conclusions

The preferential effect of dasatinib in tumor bone over normal bone is well characterized by static WB imaging using NaF PET before and while on dasatinib treatment, and was largely confirmatory of the dynamic results from these same patients [8]. The association of changes in NaF uptake while on dasatinib treatment and PFS or OS were not evident. Dasatinib had some enhanced targeting to involved disease sites but the impact on the disease overall progression was minimal. However, baseline total tumor burden and tumor volume fraction was predictive of a shorter PFS. We had hoped to observe greater effect on tumor bone, disease progression and overall survival but dasatinib showed limited efficacy as a therapeutic for mCRPC patients.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/tomography7020013/s1, Figure S1: Study design for ACRIN 6687. ^{18}F-fluoride PET was obtained at baseline before therapeutic introduction of dasatinib and at 12 $\pm$ 4 weeks into therapy. † Nilutamide-only patients are not eligible. Patients must be receiving dasatinib to be eligible. However, if a nilutamide patient crosses over at progression to add dasatinib, he may be eligible, Figure S2: The acquisition times for whole-body scans for each patient are represented by lines to indicate the variation in start time and duration of imaging of each scan for the ACRIN 6687 multi-center clinical trial. Paired lines of the same color represent the baseline scan (left) and the on-dasatinib scan (right) imaged 12 weeks later. Some patients had a different number of FOV between their two scans, Figure S3: 74-year-old patient with heterogeneous bone lesions imaged before and after dasatinib. Red box indicates the single dynamic FOV from prior report. Baseline PSA was relatively stable (pre-157, post 185) following 6 cy dasatinib (PFS was 3.0 mos). Arrows indicate the 5 hottest lesions in units of SUV_{max}. None of the 5 hottest lesions were assessed in the initial dynamic single FOV imaging study, Figure S4: The same patient described in Figure 1 using the Quantitative Total Bone Imaging (QTBI) analysis software with tumor regions outlined in red. Briefly, CT images were segmented into skeletal regions using an atlas-based approach, then region-specific optimized thresholds were used to detect lesions on the PET image segmentation A random forest model and manual review were applied to exclude lesions that were likely to be benign. The response assessment following dasatinib stratified changes in tumor uptake based off of repeatability measures (Lin 2016), Figure S5: Actual versus predicted time to progression based on multivariate regression analysis. The predicted progression model has age and baseline ln(BAP) and adds in PET SUV_{peak} as covariates. The line shows the standard deviation used for assessment of the correlation (ρ = 0.83) between true and predicted progression and determining

hazard ratios. The correlation is highly significant (p-value = 0.001), Table S1: The individual PET scanning characteristics are listed for all 18 enrolled patients in the study. Case 5 chose to withdraw from the study after the first scan. Three cases (3, 12 and 16) that progressed early, did not receive the second scan. Uptake time (UptakeT), the time between dose injection and WB scanning, is a sensitive parameter in the assessment of SUV from PET scans. The difference between the uptake times (ΔUT) shows the consistency in the protocol for the scanning institution. The iterative reconstructed image resolution for in-plane X/Y pixel size and slice thickness appears in the last two columns The BLUE highlighted cases are those reported in the original publication using the dynamic PET data. SD is the standard deviation of the group, Table S2: $SUV_{peakavg}$ and SUV_{maxavg} value is the average of up to the 5 hottest tumors that were above the threshold of 15 g/mL in the first scan. Only two patients had less than 5 tumors that met threshold criteria; Case 9 had one tumor and Case 13 had 2 tumors above the threshold. The index SUV is the hottest lesion for the patient. SD is the standard deviation of the group. Case 5 withdrew from the study, so was lost to follow-up for PFS and OS assessment, Table S3: Patient-level analysis results using QTBI software (AIQ Solutions, Inc.) for (A) scan 1 and (B) scan 2. SD is the standard deviation of the group. Case 15 had image quality and scaling issues that prevented analysis. Case 5 withdrew from the study, so was lost to follow-up for PFS and OS assessment, Table S4: Gaussian approximations for inferences using a Bootstrap approach with 500 replicates was used in univariate outcome analysis The change (Δ) while on-dastinib was determined on 14 of the 17 patients. The PFS section has correlation (tau), standard error (SE), and the p-value for each PET parameter. The OS section has the hazard ratio (HR), standard error (SE) of HR and the p-value for each PET parameter. In the analysis of overall survival, HR has the associated hazard ratio corresponding to a 1-SD increase in the PET parameter. The lesion-level analyses were performed on the average of up to 5 tumors per patient selected by uptake intensity for 17 patients at baseline. The patient-level whole-body QTBI analyses were performed on 16 patients at baseline, while change was determined on 12 of the 16 patients. Boldface type indicates a significant ($p \leq 0.05$) association with outcome.

Author Contributions: M.M.: Conceptualization, methodology, formal analysis, investigation, resources, data curation, original writing/review/editing, project administration, supervision and funding. F.O.: Statistical analysis, methodology, formal analysis, investigation, review, funding. T.G.P.: Formal analysis, QTBI PET image processing, investigation. J.P.M.: Methodology, formal analysis, VOI PET image processing, writing/review. D.A.M.: Conceptualization, formal analyses, writing/review/editing, investigation. R.J.: Formal analysis, QTBI PET image processing, investigation. F.D.: Statistical analysis, investigation. E.Y.Y.: Conceptualization, methodology, visualization, project management, supervision, writing/review/editing, funding. All authors have read and agreed to the published version of the manuscript.

Funding: The following granting agencies funded this research: National Institutes of Health Cancer Imaging Program U01-CA079778 (ACRIN; PI, Mitchell D. Schnall); R50-CA211270 (PI, M.M.); Science Foundation of Ireland PI 11/1027 (PI, F.O.).

Institutional Review Board Statement: All procedures performed in studies involving human participants were in accordance with the ethical standards of the multiple institutions' participation in ACRIN 6687 multi-center clinical trial and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This report is a secondary analysis using the data originally collected by the ACRIN clinical trial team.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the multi-center ACRIN 6687 clinical trial.

Data Availability Statement: PET image extracted data for individual patients appears in supplementary martials located on the MDPI website.

Acknowledgments: We would like to acknowledge the outstanding efforts of the ACRIN 6687 study team, which completed this multi-center clinical trial and provided the data for this report.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Coleman, R.E. Metastatic bone disease: Clinical features, pathophysiology and treatment strategies. *Cancer Treat Rev.* **2001**, *27*, 165–176. [CrossRef]

2. Jadvar, H.; Desai, B.; Conti, P.S. Sodium 18F-fluoride PET/CT of bone, joint, and other disorders. *Semin. Nucl. Med.* **2015**, *45*, 58–65. [CrossRef]
3. Harmon, S.A.; Mena, E.; Shih, J.H.; Adler, S.; McKinney, Y.; Bergvall, E.; Mehralivand, S.; Sowalsky, A.G.; Couvillon, A.; Madan, R.A.; et al. A comparison of prostate cancer bone metastases on (18)F-Sodium Fluoride and Prostate Specific Membrane Antigen ((18)F-PSMA) PET/CT: Discordant uptake in the same lesion. *Oncotarget* **2018**, *9*, 37676–37688. [CrossRef]
4. Blake, G.M.; Puri, T.; Siddique, M.; Frost, M.L.; Moore, A.E.B.; Fogelman, I. Site specific measurements of bone formation using [(18)F] sodium fluoride PET/CT. *Quant Imaging Med. Surg.* **2018**, *8*, 47–59. [CrossRef] [PubMed]
5. Even-Sapir, E.; Metser, U.; Flusser, G.; Zuriel, L.; Kollender, Y.; Lerman, H.; Lievshitz, G.; Ron, I.; Mishani, E. Assessment of malignant skeletal disease: Initial experience with 18F-fluoride PET/CT and comparison between 18F-fluoride PET and 18F-fluoride PET/CT. *J. Nucl. Med.* **2004**, *45*, 272–278. [PubMed]
6. Even-Sapir, E.; Metser, U.; Mishani, E.; Lievshitz, G.; Lerman, H.; Leibovitch, I. The detection of bone metastases in patients with high-risk prostate cancer: 99mTc-MDP Planar bone scintigraphy, single- and multi-field-of-view SPECT, 18F-fluoride PET, and 18F-fluoride PET/CT. *J. Nucl. Med.* **2006**, *47*, 287–297.
7. Tateishi, U.; Morita, S.; Taguri, M.; Shizukuishi, K.; Minamimoto, R.; Kawaguchi, M.; Murano, T.; Terauchi, T.; Inoue, T.; Kim, E.E. A meta-analysis of (18)F-Fluoride positron emission tomography for assessment of metastatic bone tumor. *Ann. Nucl. Med.* **2010**, *24*, 523–531. [CrossRef] [PubMed]
8. Yu, E.Y.; Duan, F.; Muzi, M.; Deng, X.; Chin, B.B.; Alumkal, J.J.; Taplin, M.E.; Taub, J.M.; Herman, B.; Higano, C.S.; et al. Castration-resistant prostate cancer bone metastasis response measured by 18F-fluoride PET after treatment with dasatinib and correlation with progression-free survival: Results from American College of Radiology Imaging Network 6687. *J. Nucl. Med.* **2015**, *56*, 354–360. [CrossRef] [PubMed]
9. Scher, H.I.; Halabi, S.; Tannock, I.; Morris, M.; Sternberg, C.N.; Carducci, M.A.; Eisenberger, M.A.; Higano, C.; Bubley, G.J.; Dreicer, R.; et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: Recommendations of the Prostate Cancer Clinical Trials Working Group. *J. Clin. Oncol.* **2008**, *26*, 1148–1159. [CrossRef]
10. Harmon, S.A.; Perk, T.; Lin, C.; Eickhoff, J.; Choyke, P.L.; Dahut, W.L.; Apolo, A.B.; Humm, J.L.; Larson, S.M.; Morris, M.J.; et al. Quantitative Assessment of Early [(18)F]Sodium Fluoride Positron Emission Tomography/Computed Tomography Response to Treatment in Men With Metastatic Prostate Cancer to Bone. *J. Clin. Oncol.* **2017**, *35*, 2829–2837. [CrossRef]
11. Wahl, R.L.; Jacene, H.; Kasamon, Y.; Lodge, M.A. From RECIST to PERCIST: Evolving Considerations for PET response criteria in solid tumors. *J. Nucl. Med.* **2009**, *50* (Suppl. 1), 122s–150s. [CrossRef]
12. Lin, C.; Bradshaw, T.; Perk, T.; Harmon, S.; Eickhoff, J.; Jallow, N.; Choyke, P.L.; Dahut, W.L.; Larson, S.; Humm, J.L.; et al. Repeatability of Quantitative 18F-NaF PET: A Multicenter Study. *J. Nucl. Med.* **2016**, *57*, 1872–1879. [CrossRef]
13. Kurdziel, K.A.; Shih, J.H.; Apolo, A.B.; Lindenberg, L.; Mena, E.; McKinney, Y.Y.; Adler, S.S.; Turkbey, B.; Dahut, W.; Gulley, J.L.; et al. The kinetics and reproducibility of 18F-sodium fluoride for oncology using current PET camera technology. *J. Nucl. Med.* **2012**, *53*, 1175–1184. [CrossRef]
14. Rohren, E.M.; Etchebehere, E.C.; Araujo, J.C.; Hobbs, B.P.; Swanston, N.M.; Everding, M.; Moody, T.; Macapinlac, H.A. Determination of Skeletal Tumor Burden on 18F-Fluoride PET/CT. *J. Nucl. Med.* **2015**, *56*, 1507–1512. [CrossRef]
15. Kairemo, K.; Milton, D.R.; Etchebehere, E.; Rohren, E.M.; Macapinlac, H.A. Final Outcome of 223Ra-therapy and the Role of 18F-fluoride-PET in Response Evaluation in Metastatic Castration-resistant Prostate Cancer-A Single Institution Experience. *Curr. Radiopharm.* **2018**, *11*, 147–152. [CrossRef]
16. Murray, I.; Chittenden, S.J.; Denis-Bacelar, A.M.; Hindorf, C.; Parker, C.C.; Chua, S.; Flux, G.D. The potential of (223)Ra and (18)F-fluoride imaging to predict bone lesion response to treatment with (223)Ra-dichloride in castration-resistant prostate cancer. *Eur. J. Nucl. Med. Mol. Imaging* **2017**, *44*, 1832–1844. [CrossRef] [PubMed]
17. Liu, G.; Perlman, S.; Perk, T.; Harmon, S.; Simmons, K.; Staab, M.J.; Jeraj, R. Quantitative total bone imaging (QTBI) in patients with metastatic castration-resistant prostate cancer (CRPC) using NaF PET/CT. *J. Clin. Oncol.* **2015**, *33* (Suppl. 7), 180–181. [CrossRef]
18. Yip, S.; Perk, T.; Jeraj, R. Development and evaluation of an articulated registration algorithm for human skeleton registration. *Phys. Med. Biol.* **2014**, *59*, 1485–1499. [CrossRef] [PubMed]
19. Perk, T.; Chen, S.; Harmon, S.; Lin, C.; Bradshaw, T.; Perlman, S.; Liu, G.; Jeraj, R. A statistically optimized regional thresholding method (SORT) for bone lesion detection in (18)F-NaF PET/CT imaging. *Phys. Med. Biol.* **2018**, *63*, 225018. [CrossRef]
20. Perk, T.; Bradshaw, T.; Chen, S.; Im, H.J.; Cho, S.; Perlman, S.; Liu, G.; Jeraj, R. Automated classification of benign and malignant lesions in (18)F-NaF PET/CT images using machine learning. *Phys. Med. Biol.* **2018**, *63*, 225019. [CrossRef] [PubMed]
21. Efron, B.; Tibshirani, R.J. *An Introduction to the Bootstrap*; Chapman and Hall: New York, NY, USA, 1993; Volume 57, p. 456.
22. Beaulieu, S.; Kinahan, P.; Tseng, J.; Dunnwald, L.K.; Schubert, E.K.; Pham, P.; Lewellen, B.; Mankoff, D.A. SUV varies with time after injection in (18)F-FDG PET of breast cancer: Characterization and method to adjust for time differences. *J. Nucl. Med.* **2003**, *44*, 1044–1050. [PubMed]
23. Kurland, B.F.; Muzi, M.; Peterson, L.M.; Doot, R.K.; Wangerin, K.A.; Mankoff, D.A.; Linden, H.M.; Kinahan, P.E. Multicenter Clinical Trials Using 18F-FDG PET to Measure Early Response to Oncologic Therapy: Effects of Injection-to-Acquisition Time Variability on Required Sample Size. *J. Nucl. Med.* **2016**, *57*, 226–230. [CrossRef]
24. Araujo, J.C.; Trudel, G.C.; Saad, F.; Armstrong, A.J.; Yu, E.Y.; Bellmunt, J.; Wilding, G.; McCaffrey, J.; Serrano, S.V.; Matveev, V.B.; et al. Docetaxel and dasatinib or placebo in men with metastatic castration-resistant prostate cancer (READY): A randomised, double-blind phase 3 trial. *Lancet Oncol.* **2013**, *14*, 1307–1316. [CrossRef]

25. Yu, E.Y.; Massard, C.; Gross, M.E.; Carducci, M.A.; Culine, S.; Hudes, G.; Posadas, E.M.; Sternberg, C.N.; Wilding, G.; Trudel, G.C.; et al. Once-daily dasatinib: Expansion of phase II study evaluating safety and efficacy of dasatinib in patients with metastatic castration-resistant prostate cancer. *Urology* **2011**, *77*, 1166–1171. [CrossRef] [PubMed]
26. Wang, Y.; Zhang, H.; Shen, W.; He, P.; Zhou, Z. Effectiveness and tolerability of targeted drugs for the treatment of metastatic castration-resistant prostate cancer: A network meta-analysis of randomized controlled trials. *J. Cancer Res. Clin. Oncol.* **2018**, *144*, 1751–1768. [CrossRef] [PubMed]
27. Lee, Y.C.; Huang, C.F.; Murshed, M.; Chu, K.; Araujo, J.C.; Ye, X.; deCrombrugghe, B.; Yu-Lee, L.Y.; Gallick, G.E.; Lin, S.H. Src family kinase/abl inhibitor dasatinib suppresses proliferation and enhances differentiation of osteoblasts. *Oncogene* **2010**, *29*, 3196–3207. [CrossRef]
28. Coleman, R.E.; Whitaker, K.B.; Moss, D.W.; Mashiter, G.; Fogelman, I.; Rubens, R.D. Biochemical prediction of response of bone metastases to treatment. *Br. J. Cancer* **1988**, *58*, 205–210. [CrossRef]
29. Som, A.; Tu, S.M.; Liu, J.; Wang, X.; Qiao, W.; Logothetis, C.; Corn, P.G. Response in bone turnover markers during therapy predicts overall survival in patients with metastatic prostate cancer: Analysis of three clinical trials. *Br. J. Cancer* **2012**, *107*, 1547–1553. [CrossRef] [PubMed]
30. Yasuda, Y.; Kawamura, K.; Ichikado, K.; Yoshioka, M. Alkaline phosphatase flare phenomenon following epidermal growth factor receptor-tyrosine kinase inhibitor treatment of non-small cell lung cancer: Report of a case and case review. *Respir. Med. Case Rep.* **2014**, *13*, 51–53. [CrossRef]

Published in final edited form as:

Clin Cancer Res. 2021 July 01; 27(13): 3610–3619. doi:10.1158/1078-0432.CCR-20-4616.

Phase 2 multicenter study of enzalutamide in metastatic castration resistant prostate cancer to identify mechanisms driving resistance

Rana R. McKay[1,2], **Lucia Kwak**[2], **Jett P. Crowdis**[2], **Jamie M. Sperger**[3], **Shuang G. Zhao**[3], **Wanling Xie**[2], **Lillian Werner**[2], **Rosina Lis**[2], **Zhenwei Zhang**[2], **Xiao X. Wei**[2], **Joshua M. Lang**[3], **Eliezer M. Van Allen**[2], **Rupal S. Bhatt**[4], **Evan Y. Yu**[5,6], **Peter S. Nelson**[5,6], **Glenn J. Bubley**[4], **R. Bruce Montgomery**[5,6], **Mary-Ellen Taplin**[2]

[1]University of California San Diego, San Diego, CA

[2]Dana-Farber Cancer Institute, Boston, MA

[3]Carbone Cancer Center, University of Wisconsin-Madison, Madison, WI

[4]Beth Israel Deaconess Medical Center, Boston, MA

Corresponding Author: Mary-Ellen Taplin, Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, MA 02215, US, Phone: 617-582-7221, Fax: 617-632-2165, Mary_Taplin@DFCI.harvard.edu.

Author Contribution:

Authors	Concept/ Design	Collection/Data Assembly	Data Analysis/ Interpretation	Manuscript Writing/Editing	Final Approval
RRM	X	X	X	X	X
LK	X	X	X	X	X
JPC		X	X	X	X
JMS		X	X	X	X
SGZ		X	X	X	X
WX		X	X	X	X
LW		X	X	X	X
RL		X		X	X
ZZ		X		X	X
XXW		X	X	X	X
JML		X	X	X	X
EVA		X	X	X	X
RSB		X		X	X
EYY		X		X	X
PSN		X		X	X
GJB		X		X	X
RBM		X		X	X
MET	X	X	X	X	X

[5]University of Washington, Seattle, WA

[6]Fred Hutchinson Cancer Research Center, Seattle, WA

Abstract

Purpose: Enzalutamide is a second-generation androgen receptor (AR) inhibitor which has improved overall survival (OS) in metastatic castration resistant prostate cancer (CRPC). However, nearly all patients develop resistance. We designed a phase 2 multicenter study of enzalutamide in metastatic CRPC incorporating tissue and blood biomarkers to dissect mechanisms driving resistance.

Experimental Design: Eligible patients with metastatic CRPC underwent a baseline metastasis biopsy and then initiated enzalutamide 160 mg daily. A repeat metastasis biopsy was obtained at radiographic progression from the same site when possible. Blood for circulating tumor cell (CTC) analysis was collected at baseline and progression. The primary objective was to analyze mechanisms of resistance in serial biopsies. Whole exome sequencing was performed on tissue biopsies. CTC samples underwent RNA sequencing.

Results: 65 patients initiated treatment, of whom 22 (33.8%) had received prior abiraterone. Baseline biopsies were enriched for alterations in *AR* (mutations, amplifications) and tumor suppression genes (*PTEN*, *RB1*, and *TP53*) which were observed in 73.1% and 92.3% of baseline biopsies, respectively. Progression biopsies revealed increased *AR* amplifications (64.7% at progression versus 53.9% at baseline) and *BRCA2* alterations (64.7% at progression versus 38.5% at baseline). Genomic analysis of baseline and progression CTC samples demonstrated increased AR splice variants, AR regulated-genes, and neuroendocrine markers at progression.

Conclusions: Our results demonstrate that a large proportion of enzalutamide-treated patients have baseline and progression alterations in the AR pathway and tumor suppressor genes. We demonstrate an increased number of *BRCA2* alterations post-enzalutamide highlighting importance of serial tumor sampling in CRPC.

Precis:

We report on a phase 2, multicenter, open-label, single-arm study of enzalutamide in men with metastatic castration resistant prostate cancer incorporating baseline and progression metastasis tissue sampling and serial analyses of circulating tumor cells (CTCs) to dissect mechanisms driving clinical resistance to enzalutamide. Our results demonstrate that a substantial proportion of enzalutamide-treated metastatic CRPC patients harbor alterations in the AR pathway and tumor suppressor genes which contribute to the resistance phenotype.

Keywords

Androgen receptor; Castration resistance; Circulating tumor cells; Enzalutamide; Metastases; Prostate cancer; Resistance

Introduction:

Metastatic castration resistant prostate cancer (CRPC) is a lethal disease with a relative 5-year survival of 29%.[1] While novel treatments, including androgen receptor (AR) directed therapies, have improved overall survival for patients with CRPC, resistance is observed in nearly all patients. Enzalutamide is a rationally designed second generation AR inhibitor which competitively binds to AR with great potency and also inhibits active AR nuclear translation, DNA binding, and coactivator recruitment.[2] Two large phase 3 trials demonstrated the efficacy of enzalutamide over placebo resulting in routine clinical use in metastatic CRPC.[3, 4] However, 10–25% of patients receiving enzalutamide have primary resistance and at 18-months 50–80% of patients have developed radiographic progression.[3, 4] Therefore, strategies to understand determinants of primary and acquired resistance are essential to developing therapeutic approaches to prolong the activity and durability of treatment.

Several preclinical and clinical studies have examined mechanisms of resistance to AR targeting agents. AR dependent mechanisms hypothesized to cause resistance to enzalutamide include *AR* mutations[5], amplifications[6, 7], splice variant emergence[8, 9], and altered steroidogenesis[10, 11]. Additionally, resistance may also be mediated by activation of parallel AR-independent signaling pathways[12]. While these studies have been informative, they did not integrate paired baseline and progression tumor sampling with comprehensive molecular analysis. Prospective studies embedding tumor tissue and blood-based analyses which are placed in the context of patient outcomes are needed to understand mechanisms that drive resistance to treatment. We report the results of a phase 2, multicenter, open-label, single-arm study of enzalutamide in men with metastatic CRPC incorporating baseline and progression metastasis tumor sampling and serial analyses of circulating tumor cells (CTCs) to dissect mechanisms driving *de novo* and acquired clinical resistance to enzalutamide.

Materials and Methods:

Patients:

This is a phase 2, single arm, open-label study of enzalutamide in metastatic CRPC (NCT01942837). Eligible patients had CRPC defined as disease progression despite a serum total testosterone <50 ng/dL and: 1) PSA progression as defined by the Prostate Cancer Clinical Trials Working Group (PCWG) 2[13], 2) soft tissue disease progression as defined by Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1[14], or 3) bone disease progression as defined by PCWG2[13]. Additionally, patients had evidence of metastases with at least one metastatic site amendable to biopsy. Patients were required to have prostatic adenocarcinoma. Variant histologies, including neuroendocrine differentiation, were not permitted.

Patients may have received prior hormonal therapies (including ketoconazole, abiraterone, first-generation anti-androgens) and up to two cytotoxic therapies. Prior enzalutamide, apalutamide or darolutamide was not allowed. Other eligibility criteria included an Eastern Cooperative Oncology Group performance status ≤2 and adequate organ and bone marrow

function. The study was conducted after Institutional Review Board approval at each of the participating institutions in accordance with the principals outlined in the Declaration of Helsinki. All patients provided written informed consent.

Treatment:

Following enrollment, patients had a baseline biopsy of a metastasis. Biopsies were performed after informed consent in the interventional radiology department. Subsequently, patients received enzalutamide 160 mg by mouth daily. Patients continued enzalutamide until radiographic progression, significant toxicity or patient/physician requested withdrawal. A repeat metastasis biopsy, with ongoing enzalutamide, was obtained at radiographic progression in patients completing ≥3 cycles (1 cycle=28 days). The protocol specified that when possible the progression biopsy should target the same site as the baseline biopsy. Though baseline and progression biopsies were mandatory, not all patients underwent biopsy at progression given lack of feasible biopsy site, clinical disease progression, or patient study withdrawal. Imaging assessments occurred every twelve weeks. PSA was measured every four weeks.

Tumor Tissue Genomic Sequencing:

Biopsies were prioritized for pathologic assessment followed by whole exome sequencing. Whole exome sequencing was performed on tumor biopsies and collected blood normal using a customized version of a previously described protocol.[15] After DNA shearing, hybridization and exome capture were performed using either Illumina's Rapid Capture Exome Kit or the Agilent SureSelect Human All Exon 44Mb v2.0 bait set (Supplementary Table 1S).[16] Libraries were sequenced with 76 bp paired-end reads on an Illumina instrument.

Reads were aligned using BWA v0.5.9 and somatic mutations called using a customized version of the Getz Lab CGA WES Characterization Pipeline (https://portal.firecloud.org/#methods/getzlab/CGA_WES_Characterization_Pipeline_v0.1_Dec2018/). [17] Briefly, we used ContEst to estimate contamination, MuTect and Strelka to call SNVs and indels, DeTiN to estimate tumor-in-normal contamination, and Orientation Bias Filter and MAFPoNFilter to filter sequencing artifacts.[18–23] For target intervals, we used an intersection of Illumina Rapid Capture Exome and Agilent SureSelect regions, created using bedtools.[24] Variants were annotated using VEP, Oncotator, and vcf2maf v.1.6.17 (https://github.com/mskcc/vcf2maf). [25, 26] Copy number alterations, purity, ploidy, and whole genome doubling status were called using FACETS v0.5.14.[27] In cases where FACETS fit an incorrect copy number profile, ABSOLUTE with manual review was used instead.[28] Copy number alterations were evaluated with respect to whole genome doubling status. Samples were included in the final cohort if they had contamination <4%, purity >20%, tumor coverage >50x, and normal coverage >30x. Presence of biallelic alterations was defined as 1) the presence of a loss of function mutation in addition to allelic full deletion, or 2) two allelic full deletions.

To compare mutations between distinct samples from the same patient, we used a previously described method designed to recover evidence for mutations called in one sample in all

other samples derived from the same individual.[29] In brief, the 'force-calling' method uses the strong prior of the mutation being present in at least one sample in the patient to more sensitively detect and recover mutations that might otherwise be missed. Successfully sequenced tissue samples were part of larger cohort analyses.[30, 31]

Circulating Tumor Cell Analysis:

Blood for CTC gene expression analysis was collected in vacutainer tubes (BD Biosciences) with EDTA anticoagulant at baseline and off treatment. Mononuclear cells were isolated with a Ficoll-Pacque Plus (GE Healthcare) gradient before undergoing CD45 depletion (Miltenyi Biotec). The VERSA platform[32] was used for the live cell capture of CTCs using an anti-EpCAM antibody (R&D) conjugated to paramagnetic particles (Life Technolgies). Cells were lysed in the VERSA with a modified LIDs buffer (10 mM Tris-HCL, 500 mM lithium chloride, 1 % Igepal® CA-630 (Sigma-Aldrich, USA), 5 mM ethylenediaminetetraacetic acid (EDTA), 5 mM dithiothreitol, pH 7.5) and mRNA was extracted with olgio(dt)25 Dynabeads® (Life Technologies, USA)[33].

Extracted mRNA was reverse transcribed using a High Capacity cDNA Reverse Transcriptase kit (Life Tech, USA), according to manufacturer's directions using Bio-Rad C1000 Thermo Cycler (Bio-Rad, USA). The RT reaction was amplified for 14 cycles using TaqMan® PreAmp (Life Tech) according to manufacturer's directions and diluted 1:20 in 1x TE (10 mM Tris-HCL pH8, 1 mM EDTA). For TaqMan® assays, 5 μL of diluted cDNA template was mixed with 10 μL iTaq® master mix (Bio-Rad), 1 μL TaqMan® Gene Expression Assay (Life Technologies) and 4 μL nuclease free (NF) water. Each reaction was amplified for 45 cycles (denatured at 95 °C for 15 seconds followed by annealing at 60°C for 1 minute) using a CFX Connect® Real-Time PCR System (Bio-Rad). A table of genes of interest and primers used is available in Supplementary Table 2S. Samples are reported as 38-cycle threshold value with cycle threshold values less than 38 considered positive for expression.

Statistical Analysis:

The primary objective was to analyze mechanisms of *de novo* and acquired resistance to enzalutamide in serial CRPC tumor biopsies. This was assessed by tumor exome sequencing. The trial design assumed AR related resistance parameters to be measured as continuous variable. Sample size of 40 with serial biopsies was targeted to detect a standardized effect size of 0.454 for the changes in a set of resistance parameters at progression compared to baseline having 80% power with 1-sided alpha=0.025 using the paired t-test. The planned enrollment was 66 patients to obtain 40 evaluable patients with paired samples.

Secondary endpoints included toxicity, PSA and investigator-assessed radiographic response, time to PSA and investigator-assessed radiographic progression. Toxicity was summarized using Common Terminology Criteria for Adverse Events version 4.0. Radiographic response as defined by RECIST version 1.1 was summarized with 95% exact binomial confidence interval (CI)[14]. PSA response and progression were defined by PCWG2 criteria[13]. Time to PSA progression was defined from treatment initiation to PSA

progression or censored at the date of last PSA evaluation. Radiographic progression was defined by RECIST version 1.1 for soft tissue and visceral disease and PCWG2 for bone disease[13, 14]. Progression-free survival (PFS) was defined as time from treatment initiation to radiographic progression or death from any cause, whichever came first, or censored at the date of last evaluation. Time to event endpoints were summarized using Kaplan-Meier method. We evaluated outcomes in the overall cohort, by type of prior therapy, and by CTC biomarker status. Patients with a positive CTC biomarker were defined as those positive for expression of AR variants, synaptophysin, and/or two or more AR-regulated genes (KLK2, LKL3, TMPRSS2, FOLH1, or NKX3.1). Comparisons between biomarker groups were conducted using the log-rank test.

Results:

Baseline Characteristics:

At data lock in April 2020, 67 patients were enrolled. The final analysis cohort for clinical outcomes consists of 65 men who received ≥1 dose of enzalutamide, and three patients remained on treatment; two men who never initiated treatment were excluded. Patient were enrolled between November 2013–May 2017: Dana-Farber Cancer Institute (n=39), University of Washington (n=19), Beth Israel Deaconess Medical Center (n=6), and South Shore Hospital (n=1) (Table 1). The median age was 70 years. Sixteen patients (24.6%) received prior chemotherapy, 22 (33.8%) prior abiraterone, and nine (13.8%) prior ketoconazole. All patients had metastases, of whom 32 (49.2%) had measurable disease.

PSA and Radiographic Response:

Thirty-eight patients (58.5%) achieved a ≥50% PSA reduction and 20 patients (30.8%) had a ≥90% decline in PSA (Figure 1). The PSA response rates in patients having received prior abiraterone, ketoconazole, or chemotherapy were 22.7% (n=5/22), 33.3% (n=3/9), and 68.8% (n=11/16), respectively (Supplementary Table 3S). Of the 32 patients with measurable disease, 11 (34.4%) had an objective response (Supplementary Table 4S).

PSA and Radiographic Progression:

Forty-three (66.1%) patients experienced PSA progression. Median time to PSA progression was 5.6 months (95% CI 3.7, 10.1) (Supplementary Figure 1S) in the overall cohort and 2.8 months (95% CI 1.9, 5.6; n=14 events/22 patients), 11.0 months (95% 1.8, not reached; n=5/9), and 6.4 months (95% CI 1.8, 13.8; n=10/16) in patients having received prior abiraterone, ketoconazole, and chemotherapy, respectively (Supplementary Table 5S).

Overall, 33 patients (50.8%) experienced radiographic progression. Median radiographic PFS was 11.0 months (95% CI 8.1, 19.6) (Supplementary Figure 1S): 5.3 months (95% CI 2.7, 8.1; n=13/22) for prior abiraterone (Supplementary Table 5S) and 19.1 months (95% CI 2.1, not reached) for prior chemotherapy.

Toxicity:

Patients received a median nine cycles of enzalutamide (range <1–56) with a median duration of 8.6 months (range 0.1–51.6). Five patients (7.7%) had a dose reduction to 120

mg daily and 8 patients (12.3%) experienced a treatment hold. Six patients (9.7% among 62 patients who discontinued therapy of any reason) discontinued treatment due to unacceptable toxicity.

Overall, 24.6% (n=16), 36.9% (n=24), 30.8% (n=20), and 4.6% (n=3) reported maximum grade 1, 2, 3, and 4 toxicity of any attribution. There were no grade 5 events. The most common treatment-associated adverse events of any grade included fatigue, pain, hypertension, and back pain. The most common grade 3 toxicity was hypertension. Falls occurred in six patients and all were grade 1 or 2.

Metastasis Biopsy Samples:

Overall, 66 patients underwent a baseline biopsy (including one patient who consented but did not initiate treatment) and 28 patients underwent a biopsy at progression (Supplementary Table 7S; Supplementary Figure 2S). The majority of biopsies were from bone (n=65, 68%) followed by lymph nodes (n=25, 26%). Following quality control including assessment of tumor purity, tumor and normal coverage, and contamination, successful sequencing analysis was performed on 26 (39%) baseline and 17 (61%) progression biopsies. Successful sequencing analysis was performed on 42% of bone biopsies (n=27/65) and 64% (n=16/25) of soft tissue biopsies.

Tumor Sequencing Analysis:

Androgen Receptor Alterations—Of patients with baseline biopsies (n=26), 14 (53.9%) had *AR* amplifications and seven (26.9%) had *AR* mutations of whom four (28.6%) and three patients (42.9%) had a PSA response (≥50% PSA reduction from baseline), respectively (Figure 2, Supplementary Table 8S). Of the seven *AR* mutations presents at baseline, patients with a T878S, T979A, L702H or W742L did not experience a PSA response (Supplementary Table 9S). The PSA response rate in patients without *AR* amplifications was 75% (n=9/12) and 52.6% (n=10/19) in patients without *AR* mutations. Of the nine patients who received prior abiraterone, four (44.4%) had *AR* mutations and six (66.7%) had *AR* amplifications at baseline biopsy. PSA responses to enzalutamide were low in abiraterone pretreated individuals with *AR* amplifications (n=2/6, 33.3%) or *AR* mutations (n=1/4, 25.0%).

With regards to individuals with progression biopsies (n=17), 11 patients had *AR* amplifications (64.7%) and three (17.6%) had *AR* mutations (Figure 2, Supplementary Table 8S, Supplementary Table 9S). Of the six patients who received prior abiraterone, five (83.3%) demonstrated *AR* amplifications and one (16.7%) demonstrated an *AR* mutation. PSA responses were observed in seven patients (63.6%) with *AR* amplifications and all patients with *AR* mutations at progression.

In analyzing the paired baseline and progression samples (n=10), baseline *AR* alterations [n=2 mutations (W552C, T695A), n=5 allelic amplification] were present in seven patients (70%) of whom five (71.4%) experienced a PSA response (Figure 2). The two patients who did not experience a PSA response were abiraterone exposed. Acquired *AR* alterations present in progression metastases only were observed in four patients (40%) [n=1 mutation

(S234C), n=3 allelic amplification] and all individuals experienced a PSA response to enzalutamide

Tumor Suppressor Genes Alterations—Of individuals with a baseline metastasis biopsy (n=26), alterations in tumor suppressor genes were present in 24 patients (92.3%) [*TP53* n=18 (69.2%); *RB1* n=18 (69.2%); *PTEN* n=17 (65.4%)] (Figure 2, Supplementary Table 8S). Biallelic alterations were observed in eight patients (30.7%) [*TP53* n=4/26 (15.4%); *RB1* n=1/26 (3.8%); *PTEN* n=5/26 (19.2%)]. The PSA response rate was 50.0% for patients with *TP53* alterations (n=9/18), 50.0% for *RB1* (n=9/18), and 47.1% for *PTEN* (n=8/17). The PSA response was 50% (n=4/8) in patients with biallelic alterations [*TP53* n=2/4 (50%); *RB1* n=0/1 (0%); *PTEN* n=3/5 (60%)]. PSA response rates were similar to those without tumor suppressor gene alterations [50.0% *TP53* wildtype/neutral (n=4/8), 50.0% *RB1* wildtype/neutral (n=4/8), and 55.6% *PTEN* wildtype/neutral (n=5/9)]. The frequency of tumor suppressor gene alterations was similar between patients with or without abiraterone exposure (Figure 2, Supplementary Table 8S). PSA response rates were lower in patients pretreated with abiraterone with tumor suppressor gene alterations; 25% of patients (n=2/8) pretreated with abiraterone with tumor suppressor gene alterations had a PSA response.

With regards to individuals with a progression metastasis biopsy (n=17), all patients (100%), including those with (n=6) and without (n=11) prior abiraterone exposure, had a tumor suppressor gene alteration [*TP53* n=12/17 (70.6%); *RB1* n=13/17 (76.5%); *PTEN* n=13/17 (76.5%)] (Figure 2, Supplementary Table 8S). Biallelic alterations at progression were observed in five patients (29.4%) [*TP53* n=4/17 (23.5%); *RB1* n=0/17 (0%); *PTEN* alterations n=1/17 (5.9%)]. The PSA response rate was 75.0% for patients with *TP53* alterations (n=9/12), 61.5% for *RB1* (n=8/13), and 61.5% for *PTEN* (n=8/13). The frequency of tumor suppressor gene alterations in progression biopsies was numerically higher in patients with prior abiraterone exposure compared to those naïve to abiraterone. Of patients pretreated with abiraterone with tumor suppressor gene alterations at progression (n=6), one patient (20%) experienced a PSA response.

From the paired biopsy samples (n=10), tumor suppressor gene alterations were present at baseline in nine patients (90.0%) [*TP53* n=7/10 (70.0%); *RB1* n=7/10 (70.0%); *PTEN* n=6/10 (60.0%)], including all three patients exposed to abiraterone (Figure 2). Acquired tumor suppressor gene alterations not present at baseline were observed in eight patients (80%) [(*PTEN* alteration n=4/10 (40.0%), *RB1* alteration n=4/10 (40.0%), *TP53* alteration n=2/10 (20.0%)].

DNA Repair Gene Alterations—Of individuals with a baseline biopsy (n=26), DNA repair genes alterations were present in 15 patients (57.7%) [*BRCA2* n=10/26 (38.5%); *CKD12* n=4/26 (15.4%); *ATM* n=1/26 (3.5%)] (Figure 2, Supplementary Table 8S). Biallelic alterations were observed in three patients (11.5%) [*BRCA2* n=3/26 (11.5%)]. The PSA response rate was 50.0% (n=5/10), 25% (n=1/4), and 100% (n=1/1) for patients with *BRCA2*, *CDK12*, and *ATM* alterations, respectively. The PSA response was 0% in the three patients with biallelic alterations. In wildtype/neutral patients, PSA response rates were 50.0% (n=8/16), 54.5% (n=12/22), and 48.0% (n=12/25) for patients without *BRCA2*,

CDK12, and *ATM* alterations. Of the patients pretreated with abiraterone with DNA repair alterations (n=7), only one patient (14.3%) with a *CDK12* alteration had a PSA response.

Of those with a progression metastasis biopsy (n=17), 64.7% (n=11/17) had DNA repair alteration: 64.7% *BRCA2* (n=11/17), 5.9% *CDK12* (n=1/17), and 5.9% *ATM* (n=1/17) (Figure 2, Supplementary Table 8S). PSA response rates were observed in 54.5% of patients with *BRCA2* alterations (n=6/11). One patient had a biallelic alteration in *BRCA2* and did not experience a PSA response. Of the six patients with prior abiraterone exposure and a progression biopsy, five (83.3%) had DNA repair alterations at progression (n=5/6 with *BRCA2* alterations, n=1/6 with a *CDK12* alteration), of whom two experienced a PSA response (33.3%).

From the paired metastasis samples (n=10), *BRCA2* gene alterations were observed in four patients (40.0%) at baseline (Figure 2). One patient each had a baseline *CDK12* and *ATM* alteration. Acquired *BRCA2* alterations not observed at baseline were seen in four patients (40%), in whom none were bilallelic and all co-occurred with *RB1* alterations. No patient was previously exposed to a PARP inhibitor.

SPOP and CHD1 Alterations—In the baseline biopsy samples (n=26), *SPOP* alterations were observed in nine patients (34.6%) of whom four (44.4%) experienced a PSA response (Figure 2, Supplementary Table 8S). In patients having received prior abiraterone (n=9), *SPOP* alterations were present in four individuals (44.4%) of whom two (50.0%) had a PSA response to enzalutamide. *CHD1* alterations were observed in 10 patients (38.5%) and seven (70.0%) experienced a PSA response to enzalutamide. Three patients (11.5%) had co-occurring *SPOP* and *CHD1* alterations at baseline, two (66.7%) of whom had a PSA response.

In patients with evaluable progression biopsies (n=17), *SPOP* alterations were observed in five individuals (29.4%) (Figure 2, Supplementary Table 8S). Two patients (40.0%) with progression *SPOP* alterations experienced a PSA response. *CHD1* alterations were present in nine (52.9%) patients at progression of whom seven (77.8%) had a PSA response to enzalutamide. Two patients (11.8%) had co-occurring *SPOP* and *CHD1* alterations at progression and one of these individuals experienced a PSA response.

In assessing the paired metastasis biopsies (n=10), *SPOP* alterations were present at baseline in four patients (40.0%) of whom two (50.0%) had been previously exposed to abiraterone and two (50.0%) had a PSA response to enzalutamide (Figure 2). Acquired *SPOP* alterations, not present at baseline but present at progression, were observed in two individuals (20.0%), both of whom developed emergent co-occurring *RB1* alterations and one developed emergent *AR* amplification.

Association of Tumor Gene Status with Outcomes—In evaluating baseline and progression biopsy samples, *AR* amplification was more prevalent in tumors samples at progression compared to baseline (Figure 3); no other gene was associated with presence in the progression biopsy in this analysis.

Circulating Tumor Cell Analysis:

Of the 65 patients who received at least one dose of enzalutamide, 52 had blood samples collected at baseline of whom 21 patients (40%) had adequate CTCs for gene expression analysis (Supplementary Figure 2S). Progression samples were collected from 37 patients of whom 23 (62%) had adequate samples. Reasons for the inability to perform the CTC assay for the remainder of patients included shipping delays/shipping protocol deviations (17% baseline, 5% progression) and inadequate blood volume or reagent issues (43% baseline, 22% progression). Collection methods were revised mid study that resolved these issues. Paired baseline and progression samples were available from 11 patients. Matched biopsy and CTC samples were available for six patients at baseline and 10 at progression (Supplementary Figure 3S).

We measured gene expression of splice variant AR, AR-regulated genes, and neuroendocrine markers. In swimmer plots, we observe shorter survival in patients who had detectable expression, either at baseline or progression, of genes in these pathways related to enzalutamide resistance (Figure 4). Overall survival was shorter in patients positive for enzalutamide resistant gene expression at baseline (median overall survival 17.7 months versus not reached in patients positive or negative for enzalutamide resistant gene expression respectively, HR 6.29 95% CI 1.22 to 32.5, p= 0.01) (Supplementary Figure 4S). When comparing the paired baseline and progression CTC samples (n=11), there was increased frequency of AR splice variants, AR regulated genes, and neuroendocrine markers in progression samples compared to baseline (Figure 5).

Discussion:

In this phase 2 study, embedding tissue and CTC-based genomic analyses, we investigate mechanisms of resistance to enzalutamide in metastatic CRPC. This analysis is important to understanding therapy selection and developing strategies to overcome resistance. Our analysis of tumor genomics with tissue and blood-based assays, confirms the landscape of CRPC alterations and reveals several insights about mechanisms of resistance to enzalutamide.[30]

A critical initial step to the molecular characterization of metastatic CRPC is the procurement of tumor tissue for genomic profiling. Successful sequencing of a metastasis biopsy requires sufficient tumor for isolation of high-quality nucleic acid. The majority of prostate cancer patients have bone metastases and bone-predominant disease. Bone metastases are frequently associated with a dense sclerotic reaction making biopsy itself and DNA preparation technically challenging; decalcification procedures may have a negative impact on nucleic acid quality and quantity. While use of archival primary prostate tumor tissue could overcome some of these challenges, treatment-naïve tumors will not capture alterations that emerge as a consequence of systemic therapy.[34]

In our study, of the 94 biopsies performed, 46% underwent successful whole exome sequencing. Larger efforts profiling the genomic landscape of metastatic CRPC, either do not report on successful sequencing yield from patients who underwent metastasis biopsy or report slightly higher yields than documented in our series.[30, 31, 35] Ongoing refinement

of tissue biopsy and processing procedures will maximize the success of future genomic analyses in CRPC; these efforts are especially important in the current era of PARP inhibitor therapy. Given the challenges associated with metastasis biopsy and limitations in capturing the scope of tumor heterogeneity from an isolated metastatic site, minimally invasive blood-based “liquid” biopsies have emerged as an alternative to tissue sampling. Liquid biopsies enable frequent and sequential monitoring of tumor molecular dynamics; however, the concordance of tissue and blood-based methods for genomic assessment has varied.[36] In our study, we utilize an integrated molecular CTC assay to complement tissue analyses. Of the 89 patients with blood samples collected for CTC analysis, 49% underwent successful gene expression analysis. Because of an initial low success rate, we refined our methods for sample collection, shipping, and processing which resulted in higher yields in collected progression samples.

While only 25% of patients in our cohort (n=16/65) had biopsies with matched CTC analysis and the methodologies of analysis differed by specimen source, there were notable similarities in tissue and CTC molecular profiles. Specimens with *AR* alterations in tissue had increased expression of AR and AR regulated genes in CTCs. Our work aligns with other studies demonstrating conservation of AR alterations between CTCs and biopsies suggesting that CTCs can serve as a non-invasive surrogate for characterizing tumor molecular alterations.[37–39]

We demonstrate that *BRCA2* alterations were acquired in 40% (n=4/10) of patients with paired metastasis biopsies following treatment with enzalutamide. Whether these alterations are true driver events remains to be determined given that most were monoallelic losses co-occurring with *RB1* alterations. Prior reports have demonstrated the presence of alterations in homologous recombination repair (HRR) genes in tumors post AR signaling inhibitors (ARSIs), however these reports were without analysis of tumor samples prior to ARSI exposure.[31] *BRCA2* and *RB1* are both located on chromosome 13q, 16 megabases apart, thus there is a tendency for co-occurrence of alterations in these genes.[30] Moreover, while our numbers are small, these data underscore the value of serial tumor sampling in patients with CRPC to identify potential molecular targets with vulnerabilities to systemic treatment and also to evaluate for the emergence of neuroendocrine prostate cancer. Patients with HRR alterations, particularly *BRCA2* mutations, can be responsive to PARP inhibitors or platinum chemotherapy, therefore testing for the emergence of such alterations is critical to therapy selection for patients. Our RNA-based CTC assay did not integrate HRR gene status, though continued assay refinement to integrate assessment of DNA and RNA is currently in process.

We confirm that AR pathway alterations, namely amplifications and mutations, are drivers of resistance to enzalutamide. Point mutations in the *AR* ligand-binding domain have been associated with resistance to AR-targeted therapy, including F877L and T878A, which have been associated with resistance to ARSIs.[5, 40–42] Other mutations, including T878S, have been associated with receptor promiscuity with increased sensitivity to steroids or AR antagonists.[42] L702H has been observed to emerge following glucocorticoid exposure and confers resistance to enzalutamide.[43] In our study, patients harboring baseline T878A, T878S, W742L, and L702H did not have a PSA response to enzalutamide. This raises the question of whether alternate AR antagonists, such as darolutamide, which have

demonstrated *in vitro* activity against mutant *AR*, would be more effective in metastatic CPRC harboring these mutations or in the post abiraterone setting.[44] Our work highlights the difficulty of individual real-time tumor analysis, however targeted patient/tumor specific therapy remains a laudable goal.

We demonstrate that CTC transcriptomic interrogation is feasible and results in meaningful information that can elucidate both primary and secondary resistance mechanisms to enzalutamide. The CTC gene set analyzed in this cohort included splice variant *AR*, *AR* regulated genes, and neuroendocrine markers. While the well-studied AR variant-7 has clinical relevance given that detection in CTCs is predictive of resistance to enzalutamide and abiraterone, additional AR variants have been discovered that confer resistance to ARSIs[45]. In our CTC analysis, expression of AR variants and AR-regulated genes was seen in a higher proportion of progression CTC samples, consistent with findings observed from tumor genomic profiling. Given that CTCs are shed from tumor into circulation, it is expected that some concordance between tissue and CTC profiling would exist. Prior studies have demonstrated conservation between CTC and tissue AR pathway alterations, including AR variants and amplifications.[38] We confirm that possible AR dependency remains a persistent mechanism of resistance in CPRC and can be recapitulated in CTC analysis.

It is recognized that a proportion of CRPC tumors develop histologic neuroendocrine transformation as an AR-independent mechanism of treatment resistance. These tumors often have low or absent AR and/or AR-regulated genes and increased expression of classic neuroendocrine markers, including chromogranin and synaptophysin[46]. Frequently, these tumors harbor loss of *RB1* and *TP53*, however these alterations are not specific to neuroendocrine CRPC[47]. In our CTC analysis, we demonstrate that progression samples exhibit increased expression of markers of resistance including neuroendocrine markers, AR variants but also increase in AR-regulated genes. This result likely reflects the heterogeneity of both AR-dependent and independent resistance mechanisms observed in advanced CRPC and lineage plasticity occurring in a subset of resistance clones. ARSI exposed tumors have a higher percentage of histologic neuroendocrine features and have higher neuroendocrine expression scores[30]. A recent study demonstrated that a targeted genomic and epigenomic gene set applied to cfDNA was capable of identifying patients with neuroendocrine CRPC with high concordance between cfDNA and tissue[48]. Patients with neuroendocrine CPRC are candidates for platinum chemotherapy, although subsequent effective treatments are limited for this poor risk population.

We evaluate the relevance of *SPOP* alterations in baseline and progression samples and demonstrate a PSA response rate of 55% (n=6/11) in patients with baseline *SPOP* alterations. Furthermore, two of the three abiraterone pretreated patients with *SPOP* alterations demonstrated a response to enzalutamide. Prior studies have demonstrated that *SPOP*-mutated prostate cancer is associated with more favorable prognosis, enrichment in earlier stage disease relative to CRPC, and improved responses to ARSI[30]. While our numbers are low, our data corroborate these findings.

Lastly, we confirm that prior exposure to CYP-17 inhibition, including abiraterone or ketoconazole, results in blunted efficacy to enzalutamide. In patients without abiraterone

and/or ketoconazole exposure, PSA ≥50% responses were observed in 79.5% (n=31/39), while 26.9% of abiraterone and/or ketoconazole exposed patients (n=7/26) and 13.2% of abiraterone exposed patient (n=5/22) experienced a PSA response. This is consistent with prior studies which have demonstrated that sequential use of ARSIs results in cross-resistance and decreased efficacy[49, 50]. In a randomized, phase 2 crossover trial evaluating abiraterone followed by enzalutamide, PSA responses to second-line enzalutamide were seen in 36% of patients compared to 68% in patients receiving first-line abiraterone[49]. Additionally, a meta-analysis of eight studies including 643 patients demonstrated decreased PSA responses to second-line ARSIs[50].

Despite this being a prospective, multicenter phase 2 study interrogating mechanisms of resistance to enzalutamide, several limitations exist. The study required blood and tissue collection at baseline and progression; however, samples passing quality control were limited, resulting in a smaller sample size than projected. Additionally, the small sample size limited our ability to make inferences regarding less common genomic events.

Despite limitations our results confirm previously published data that resistance to enzalutamide is driven by alterations in the AR pathway and tumor suppressor genes. Our work was performed within the framework of a prospective, multicenter phase 2 trial leveraging paired tissue sampling and minimally invasive liquid biopsies in a patient population representative of standard enzalutamide treatment. Larger prospective studies, with integrated tissue analyses, are ongoing to validate the CTC gene expression panel utilized in this study. This panel has the potential to guide therapy selection between AR targeting agents, PARP inhibitors, chemotherapy, and clinical trials. Our data underscore the need for novel treatments and combinations to enhance efficacy to AR targeting agents and overcome or prolong resistance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

We would like to thank the patients and family members who participated in this clinical trial. This study was funded by Medivation/Astellas (M. Taplin). It was also supported by the Fairweather Family Fund (P. Taplin) and Fat Boys Slim Sisters Fund (M. Taplin) at the Lank Center for Genitourinary Oncology DFCI, PCF Challenge Award (Award Number 16CHAL03 – M. Taplin), and the National Cancer Institute (Award Numbers P01CA163227, R01CA234715 and the DH/HCC Prostate Cancer SPORE NCI P50 CA090381 – M. Taplin; PNW Prostate Cancer Spore NCI P50 CA097186 – P. Nelson).

Conflict of Interest:

RRM received research funding from Bayer, Pfizer, Tempus; serves on Advisory Board for AstraZeneca, Bayer, Bristol Myers Squibb, Calithera, Exelixis, Janssen, Merck, Novartis, Pfizer, Sanofi, Tempus; is a consultant for Dendreon, Vividion. PSN served received renumeration for consultant/advisory services to Bristol Myers Squibb, Astellas, and Janssen. XW received research funding from Bristol Myers Squibb. EMV received renumeration for consultant/advisory services to Tango Therapeutics, Genome Medical, Invitae, Enara Bio, Janssen, Manifold Bio, Monte Rosa, and received research funding from Novartis, Bristol Myers Squibb. MET served on the Advisory Board for Bayer, AstraZeneca, Janssen, Abbvie, and Astellas. The remaining authors have no disclosures.

References:

1. Sartor O, de Bono JS. Metastatic Prostate Cancer. N Engl J Med 2018; 378: 1653–1654.
2. Tran C, Ouk S, Clegg NJ et al. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. Science 2009; 324: 787–790. [PubMed: 19359544]
3. Beer TM, Armstrong AJ, Rathkopf DE et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014; 371: 424–433. [PubMed: 24881730]
4. Scher HI, Fizazi K, Saad F et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012; 367: 1187–1197. [PubMed: 22894553]
5. Joseph JD, Lu N, Qian J et al. A clinically relevant androgen receptor mutation confers resistance to second-generation antiandrogens enzalutamide and ARN-509. Cancer Discov 2013; 3: 1020–1029. [PubMed: 23779130]
6. Conteduca V, Wetterskog D, Sharabiani MTA et al. Androgen receptor gene status in plasma DNA associates with worse outcome on enzalutamide or abiraterone for castration-resistant prostate cancer: a multi-institution correlative biomarker study. Ann Oncol 2017; 28: 1508–1516. [PubMed: 28472366]
7. Edwards J, Krishna NS, Grigor KM, Bartlett JM. Androgen receptor gene amplification and protein expression in hormone refractory prostate cancer. Br J Cancer 2003; 89: 552–556. [PubMed: 12888829]
8. Antonarakis ES, Lu C, Wang H et al. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. N Engl J Med 2014; 371: 1028–1038. [PubMed: 25184630]
9. Armstrong AJ, Halabi S, Luo J et al. Prospective Multicenter Validation of Androgen Receptor Splice Variant 7 and Hormone Therapy Resistance in High-Risk Castration-Resistant Prostate Cancer: The PROPHECY Study. J Clin Oncol 2019; 37: 1120–1129. [PubMed: 30865549]
10. Liu C, Lou W, Zhu Y et al. Intracrine Androgens and AKR1C3 Activation Confer Resistance to Enzalutamide in Prostate Cancer. Cancer Res 2015; 75: 1413–1422. [PubMed: 25649766]
11. Stanbrough M, Bubley GJ, Ross K et al. Increased expression of genes converting adrenal androgens to testosterone in androgen-independent prostate cancer. Cancer Res 2006; 66: 2815–2825. [PubMed: 16510604]
12. Crona DJ, Whang YE. Androgen Receptor-Dependent and -Independent Mechanisms Involved in Prostate Cancer Therapy Resistance. Cancers (Basel) 2017; 9.
13. Scher HI, Halabi S, Tannock I et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 2008; 26: 1148–1159. [PubMed: 18309951]
14. Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228–247. [PubMed: 19097774]
15. Fisher S, Barry A, Abreu J et al. A scalable, fully automated process for construction of sequence-ready human exome targeted capture libraries. Genome Biol 2011; 12: R1. [PubMed: 21205303]
16. Gnirke A, Melnikov A, Maguire J et al. Solution hybrid selection with ultra-long oligonucleotides for massively parallel targeted sequencing. Nat Biotechnol 2009; 27: 182–189. [PubMed: 19182786]
17. Li H, Durbin R. Fast and accurate short read alignment with Burrows-Wheeler transform. Bioinformatics 2009; 25: 1754–1760. [PubMed: 19451168]
18. Cibulskis K, Lawrence MS, Carter SL et al. Sensitive detection of somatic point mutations in impure and heterogeneous cancer samples. Nat Biotechnol 2013; 31: 213–219. [PubMed: 23396013]
19. Cibulskis K, McKenna A, Fennell T et al. ContEst: estimating cross-contamination of human samples in next-generation sequencing data. Bioinformatics 2011; 27: 2601–2602. [PubMed: 21803805]
20. Costello M, Pugh TJ, Fennell TJ et al. Discovery and characterization of artifactual mutations in deep coverage targeted capture sequencing data due to oxidative DNA damage during sample preparation. Nucleic Acids Res 2013; 41: e67. [PubMed: 23303777]

21. Lawrence MS, Stojanov P, Mermel CH et al. Discovery and saturation analysis of cancer genes across 21 tumour types. Nature 2014; 505: 495–501. [PubMed: 24390350]
22. Saunders CT, Wong WS, Swamy S et al. Strelka: accurate somatic small-variant calling from sequenced tumor-normal sample pairs. Bioinformatics 2012; 28: 1811–1817. [PubMed: 22581179]
23. Taylor-Weiner A, Stewart C, Giordano T et al. DeTiN: overcoming tumor-in-normal contamination. Nat Methods 2018; 15: 531–534. [PubMed: 29941871]
24. Quinlan AR, Hall IM. BEDTools: a flexible suite of utilities for comparing genomic features. Bioinformatics 2010; 26: 841–842. [PubMed: 20110278]
25. McLaren W, Gil L, Hunt SE et al. The Ensembl Variant Effect Predictor. Genome Biol 2016; 17: 122. [PubMed: 27268795]
26. Ramos AH, Lichtenstein L, Gupta M et al. Oncotator: cancer variant annotation tool. Hum Mutat 2015; 36: E2423–2429. [PubMed: 25703262]
27. Shen R, Seshan VE. FACETS: allele-specific copy number and clonal heterogeneity analysis tool for high-throughput DNA sequencing. Nucleic Acids Res 2016; 44: e131. [PubMed: 27270079]
28. Carter SL, Cibulskis K, Helman E et al. Absolute quantification of somatic DNA alterations in human cancer. Nat Biotechnol 2012; 30: 413–421. [PubMed: 22544022]
29. Stachler MD, Taylor-Weiner A, Peng S et al. Paired exome analysis of Barrett's esophagus and adenocarcinoma. Nat Genet 2015; 47: 1047–1055. [PubMed: 26192918]
30. Abida W, Cyrta J, Heller G et al. Genomic correlates of clinical outcome in advanced prostate cancer. Proc Natl Acad Sci U S A 2019; 116: 11428–11436. [PubMed: 31061129]
31. Robinson D, Van Allen EM, Wu YM et al. Integrative clinical genomics of advanced prostate cancer. Cell 2015; 161: 1215–1228. [PubMed: 26000489]
32. Sperger JM, Strotman LN, Welsh A et al. Integrated Analysis of Multiple Biomarkers from Circulating Tumor Cells Enabled by Exclusion-Based Analyte Isolation. Clin Cancer Res 2017; 23: 746–756. [PubMed: 27401243]
33. Strotman L, O'Connell R, Casavant BP et al. Selective nucleic acid removal via exclusion (SNARE): capturing mRNA and DNA from a single sample. Anal Chem 2013; 85: 9764–9770. [PubMed: 24016179]
34. van Dessel LF, van Riet J, Smits M et al. The genomic landscape of metastatic castration-resistant prostate cancers reveals multiple distinct genotypes with potential clinical impact. Nat Commun 2019; 10: 5251. [PubMed: 31748536]
35. Sailer V, Schiffman MH, Kossai M et al. Bone biopsy protocol for advanced prostate cancer in the era of precision medicine. Cancer 2018; 124: 1008–1015. [PubMed: 29266381]
36. Wyatt AW, Annala M, Aggarwal R et al. Concordance of Circulating Tumor DNA and Matched Metastatic Tissue Biopsy in Prostate Cancer. J Natl Cancer Inst 2017; 109.
37. Josefsson A, Larsson K, Mansson M et al. Circulating tumor cells mirror bone metastatic phenotype in prostate cancer. Oncotarget 2018; 9: 29403–29413. [PubMed: 30034626]
38. Podolak J, Eilers K, Newby T et al. Androgen receptor amplification is concordant between circulating tumor cells and biopsies from men undergoing treatment for metastatic castration resistant prostate cancer. Oncotarget 2017; 8: 71447–71455. [PubMed: 29069718]
39. Punnoose EA, Ferraldeschi R, Szafer-Glusman E et al. PTEN loss in circulating tumour cells correlates with PTEN loss in fresh tumour tissue from castration-resistant prostate cancer patients. Br J Cancer 2015; 113: 1225–1233. [PubMed: 26379078]
40. Chen EJ, Sowalsky AG, Gao S et al. Abiraterone treatment in castration-resistant prostate cancer selects for progesterone responsive mutant androgen receptors. Clin Cancer Res 2015; 21: 1273–1280. [PubMed: 25320358]
41. Rathkopf DE, Smith MR, Ryan CJ et al. Androgen receptor mutations in patients with castration-resistant prostate cancer treated with apalutamide. Ann Oncol 2017; 28: 2264–2271. [PubMed: 28633425]
42. Taplin ME, Bubley GJ, Ko YJ et al. Selection for androgen receptor mutations in prostate cancers treated with androgen antagonist. Cancer Res 1999; 59: 2511–2515. [PubMed: 10363963]
43. Carreira S, Romanel A, Goodall J et al. Tumor clone dynamics in lethal prostate cancer. Sci Transl Med 2014; 6: 254ra125.

44. Yu J, Zhou P, Hu M et al. Discovery and biological evaluation of darolutamide derivatives as inhibitors and down-regulators of wild-type AR and the mutants. Eur J Med Chem 2019; 182: 111608. [PubMed: 31437779]
45. Tietz KT, Dehm SM. Androgen receptor variants: RNA-based mechanisms and therapeutic targets. Hum Mol Genet 2020; 29: R19–R26. [PubMed: 32412639]
46. Epstein JI, Amin MB, Beltran H et al. Proposed morphologic classification of prostate cancer with neuroendocrine differentiation. Am J Surg Pathol 2014; 38: 756–767. [PubMed: 24705311]
47. Beltran H, Rickman DS, Park K et al. Molecular characterization of neuroendocrine prostate cancer and identification of new drug targets. Cancer Discov 2011; 1: 487–495. [PubMed: 22389870]
48. Beltran H, Romanel A, Conteduca V et al. Circulating tumor DNA profile recognizes transformation to castration-resistant neuroendocrine prostate cancer. J Clin Invest 2020; 130: 1653–1668. [PubMed: 32091413]
49. Khalaf DJ, Annala M, Taavitsainen S et al. Optimal sequencing of enzalutamide and abiraterone acetate plus prednisone in metastatic castration-resistant prostate cancer: a multicentre, randomised, open-label, phase 2, crossover trial. Lancet Oncol 2019; 20: 1730–1739. [PubMed: 31727538]
50. Mori K, Miura N, Mostafaei H et al. Sequential therapy of abiraterone and enzalutamide in castration-resistant prostate cancer: a systematic review and meta-analysis. Prostate Cancer Prostatic Dis 2020.

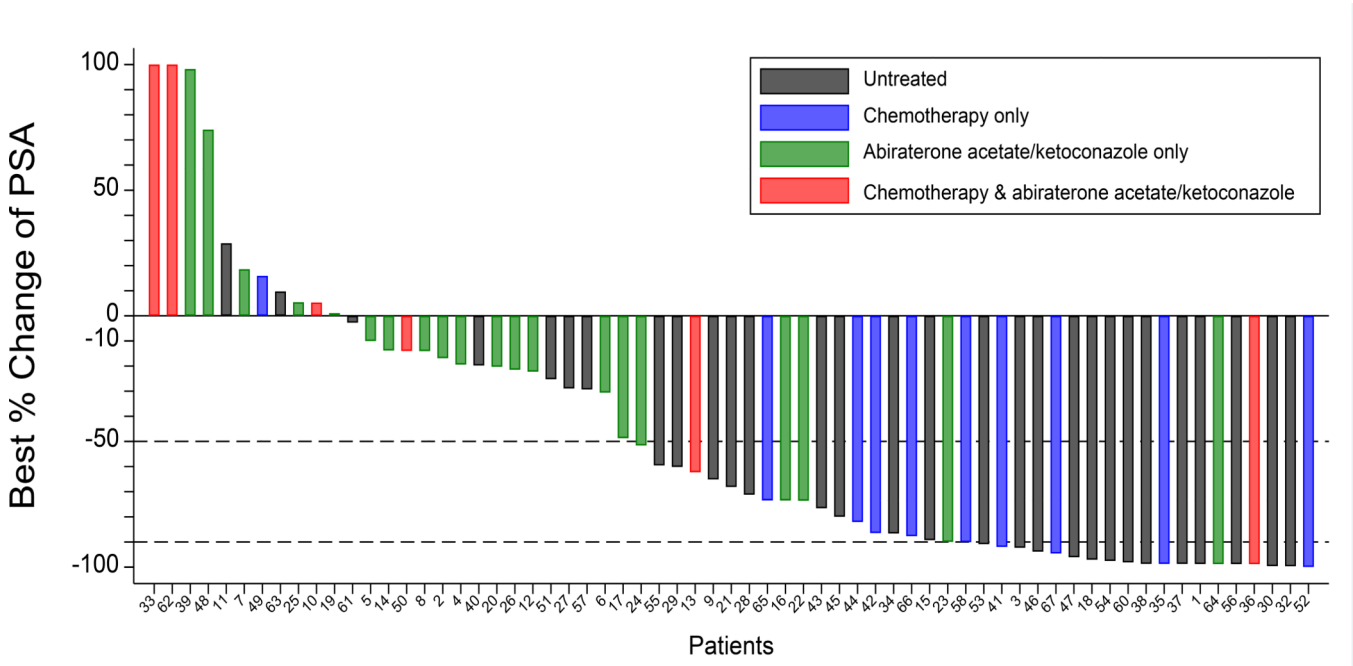


Figure 1. Waterfall plot of best PSA response to therapy with enzalutamide.

Each bar represents an individual patient. Best percent change of PSA was calculated using date of first cycle of PSA as reference. Each green, blue and red bar indicates those who received prior therapies of abiraterone acetate/ketoconazole only (n=20), chemotherapy only (n=10) and both (n=6), respectively. The gray bars represent patients without prior treatment with chemotherapy, abiraterone acetate, or ketoconazole.

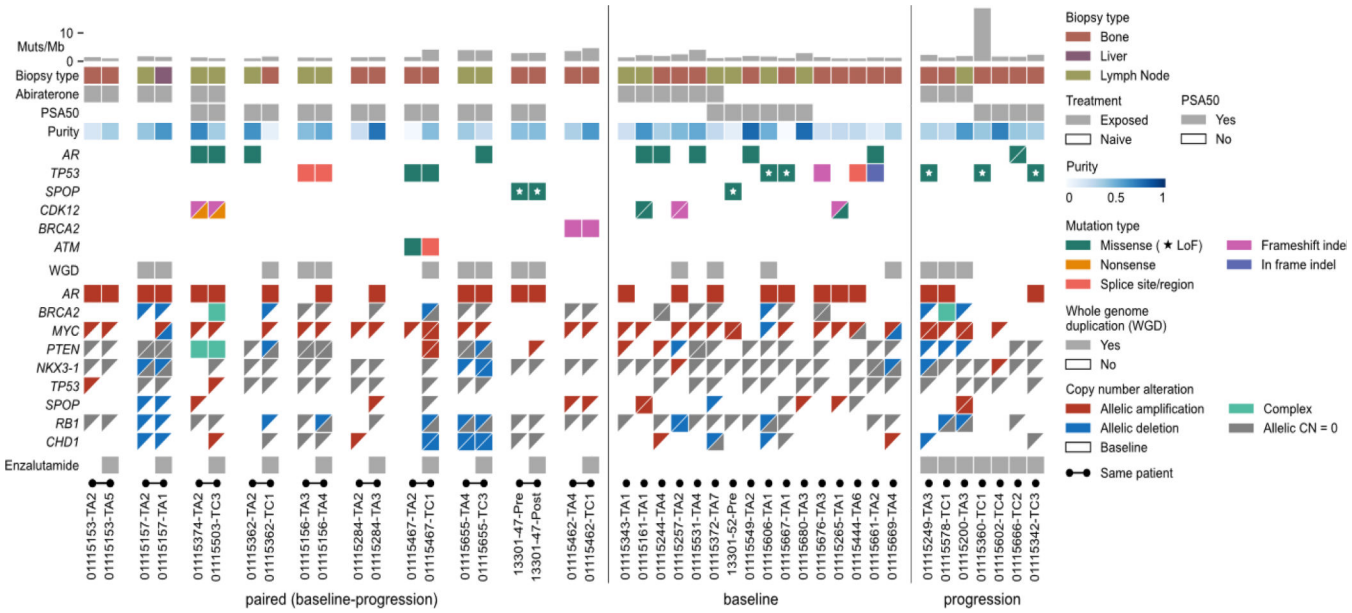


Figure 2. Integrative landscape analysis of somatic alterations obtained through DNA sequencing from baseline metastasis biopsies prior to treatment with enzalutamide and progression metastasis biopsies following treatment with enzalutamide.

Columns represent an individual metastasis biopsy. The left panel of columns represents paired baseline and progression metastasis biopsies obtained from the same individual (total 10 patients). The middle panel represents baseline biopsies only (total 16 patients). The right panel represents progression biopsies only (total 7 patients). Mutations per Mb are shown in the upper histogram. Biopsy type, prior abiraterone exposure, and presence of PSA ≥50% response from baseline are delineated in the first three rows. The remaining rows represent specific genes of interest. Color legend of the alterations are displayed. Multiple mutations in a gene are represented by triangles. Copy number calls are allelic and relative to whole genome doubling status, with calls for the two alleles indicated by two triangles. Allelic deletions that are not complete deletions are possible in samples with whole genome doubling. Because *AR* is on the X chromosome and has only a single allele in men, its copy number is represented as a box. Complex indicates that a copy number breakpoint occurred within the body of the gene. Putative loss of function (LoF) missense mutations were annotated as LoF or likely LoF in OncoKB or mutated the same amino acid as a LoF mutation. This plot was created using the CoMut software.

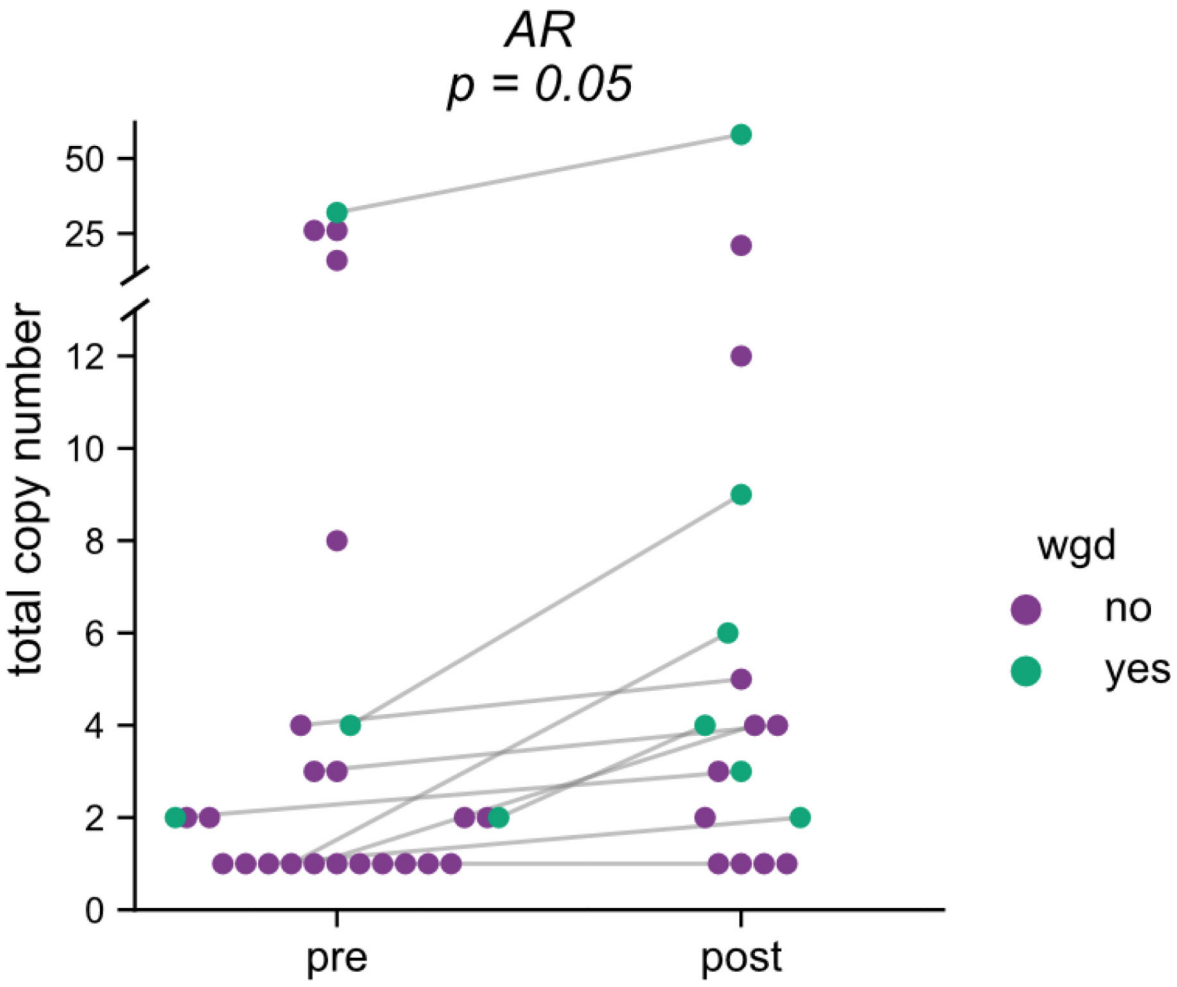


Figure 3. Association of AR amplification in progression samples (n=17) compared to baseline samples (n=26).

To assess significant changes in copy number before and after enzalutamide exposure, we combined p-values from a paired, two-sided Mann-Whitney U test for paired biopsies (n=10 pairs) and an unpaired, two-sided Mann-Whitney U test using unpaired biopsies (n=16 baseline, n=7 progression). The p-values were combined using a partially-mixed pooling approach designed to enable robust analysis of combined paired and unpaired data. AR=Androgen receptor, WGD=Whole genome duplication.

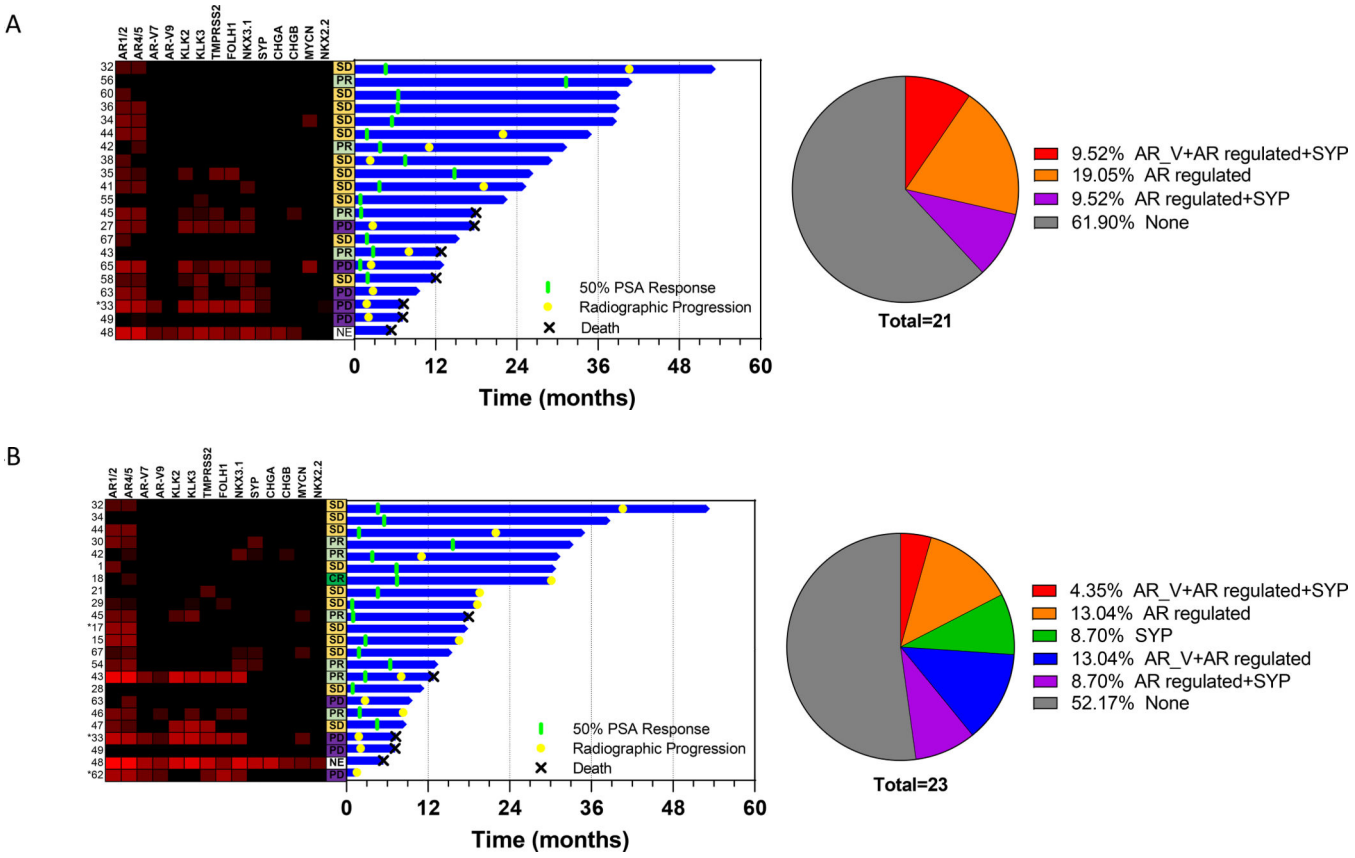


Figure 4. CTC gene expression analysis at baseline (A) and at progression (B).

Left panel: Heatmap showing expression of genes of interest. Each row represents an individual patient. Each column represents an individual gene. Red denotes increased expression. Middle panel: Swimmer plot of patient outcomes. Each row represents an individual patient. Column to the left of the Swimmer plot denotes best objective response on radiographic imaging (PR=partial response; SD=stable disease; PD=progressive disease). Right panel: Pie chart demonstrating percent expression of *AR* splice variants, AR regulated genes, and synaptophysin.

A) Baseline CTC expression analysis correlated with patient outcomes.

B) Progression CTC expression analysis correlated with patient outcomes.

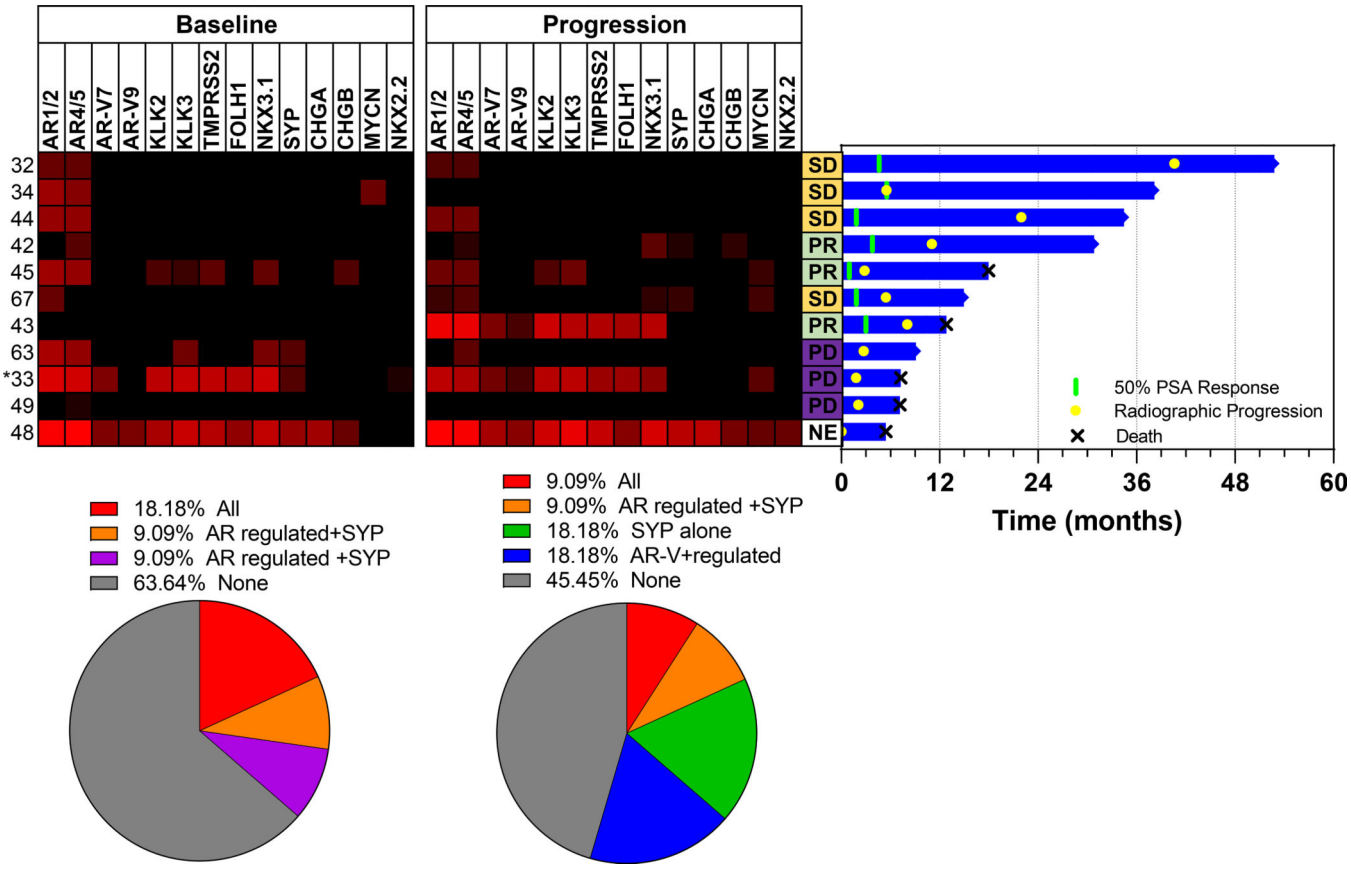


Figure 5. CTC gene expression analysis of paired baseline and progression samples.

A: Heatmaps showing expression of genes of interest. Each row represents an individual patient. Each column represents an individual gene. Red denotes increased expression. Left panel denotes baseline pre-treatment CTC samples. Right panel denotes progression CTC samples. B: Pie chart demonstrating percent expression of *AR* splice variants, synaptophysin, and AR regulated genes. Left pie chart denotes baseline pre-treatment CTC samples. Right pie chart denotes progression CTC samples. C: Swimmer plot of patient outcomes. Each row represents an individual patient. Column to the left of the Swimmer plot denotes best objective response on radiographic imaging (PR=partial response; SD=stable disease; PD=progressive disease).

Table 1.

Baseline patient and disease characteristics.

Characteristic	N	Median (q1-q3) or %
Institution		
Dana-Farber Cancer Institute	39	60.0%
University of Washington	19	29.2%
Beth Israel Deaconess Medical Center	6	9.2%
South Shore Hospital	1	1.5%
Age at baseline (years)	65	70 (66–75)
ECOG performance status		
0	44	67.7%
1	21	32.3%
Gleason score at diagnosis		
6	6	9.2%
7	22	33.8%
8	9	13.8%
9	22	33.8%
10	3	4.6%
Missing	3	4.6%
Metastases at diagnosis	18	27.7%
Prior chemotherapy	16	24.6%
Prior docetaxel	15	23.1%
Prior abiraterone *	22	33.8%
Prior ketoconazole	9	13.8%
Prior sipuleucel-T	15	23.1%
Prior first-generation anti-androgens **	53	81.5%
Measureable disease at baseline	32	49.2%
Non-measurable disease at baseline	65	100%
Sites of metastasis at baseline ***		
Bone	58	89.2%
Lymph nodes	32	49.2%
Lung	8	12.3%
Liver	1	1.5%
Other ****	9	13.8%

Characteristic	N	Median (q1-q3) or %
Laboratory data at baseline		
PSA (ng/mL)	65	14.2 (6.9–140.6)
Albumin (g/dL)	65	4.2 (4.0–4.4)
Alkaline phosphatase (U/L)	65	80 (66–116)
Calcium (mg/dL)	65	9.6 (9.2–9.8)
Hemoglobin (g/dL)	65	12.8 (11.7–13.6)
Platelets (K/UL)	65	211 (183–268)
White blood cells (K/uL)	65	6.4 (5.5–7.6)

ECOG=Eastern Oncology Cooperative Group, PSA=prostate specific antigen.

*17 patients received prior abiraterone without ketoconazole; 5 patients received prior abiraterone and ketoconazole.

**First-generation anti-androgens include bicalutamide or nilutamide,

***Percentage for each category is calculated based on N=65, regardless of measurable/non-measurable disease.

****Others include bladder, pelvis, paraspinal lesion, peritoneum/omentum or prostate.

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Prostate Cancer

Editorial by Maxton E. Thoman, Keyan Salari on pp. 31–33 of this issue

Pembrolizumab Plus Docetaxel and Prednisone in Patients with Metastatic Castration-resistant Prostate Cancer: Long-term Results from the Phase 1b/2 KEYNOTE-365 Cohort B Study

Evan Y. Yu [a,], Michael P. Kolinsky [b], William R. Berry [c], Margitta Retz [d], Loic Mourey [e], Josep M. Piulats [f], Leonard J. Appleman [g], Emanuela Romano [h], Gwenaelle Gravis [i], Howard Gurney [j], Martin Bögemann [k], Urban Emmenegger [l], Anthony M. Joshua [m], Mark Linch [n], Srikala Sridhar [o], Henry J. Conter [p], Brigitte Laguerre [q], Christophe Massard [r,s], Xin Tong Li [t], Charles Schloss [t], Christian H. Poehlein [t], Johann S. de Bono [u]*

[a] *Department of Medicine, Division of Oncology, University of Washington and Fred Hutchinson Cancer Research Center, G4-830, Seattle, WA, USA;* [b] *Department of Oncology, Cross Cancer Institute, Edmonton, AB, Canada;* [c] *Department of Medical Oncology, Duke Cancer Center Cary, Cary, NC, USA;* [d] *Department of Urology, Rechts der Isar Medical Center, Technical University of Munich, Munich, Germany;* [e] *Department of Medical Oncology, Institut Universitaire du Cancer de Toulouse – Oncopole, Toulouse, France;* [f] *Department of Medical Oncology, Catalan Institute of Oncology, Barcelona, Spain;* [g] *Department of Hematology/Oncology, Department of Medicine, University of Pittsburgh, Pittsburgh, PA, USA;* [h] *Department of Medical Oncology, Center for Cancer Immunotherapy, Institut Curie, Paris, France;* [i] *Department of Medical Oncology, Institut Paoli Calmettes, Aix-Marseille Université, Marseille, France;* [j] *Department of Medical Oncology, Macquarie University, Sydney, NSW, Australia;* [k] *Department of Urology, University Hospital Münster, Münster, Germany;* [l] *Division of Medical Oncology, Odette Cancer Centre and Sunnybrook Research Institute, Toronto, ON, Canada;* [m] *Department of Medical Oncology, Kinghorn Cancer Centre, St Vincent's Hospital, Sydney, NSW, Australia;* [n] *Department of Oncology, University College London Hospital and UCL Cancer Institute, London, UK;* [o] *Cancer Clinical Research Unit, UHN Princess Margaret Cancer Centre, Toronto, ON, Canada;* [p] *Department of Medical Oncology, University of Western Ontario, Brampton, ON, Canada;* [q] *Department of Medical Oncology, Centre Eugene Marquis, Rennes, France;* [r] *Department of Drug Development, Gustave Roussy Cancer Campus and Université Paris-Sud, Villejuif, France;* [s] *Department of Medical Oncology, Gustave Roussy Cancer Campus and Université Paris-Sud, Villejuif, France;* [t] *Department of Medical Oncology, Merck & Co., Inc., Kenilworth, NJ, USA;* [u] *Division of Clinical Studies, The Royal Marsden Hospital and The Institute of Cancer Research, London, UK*

Article info

Article history:
Accepted February 22, 2022

Associate Editor:
James Catto

Abstract

Background: Patients with metastatic castration-resistant prostate cancer (mCRPC) frequently receive docetaxel after they develop resistance to abiraterone or enzalutamide and need more efficacious treatments.
Objective: To evaluate the efficacy and safety of pembrolizumab plus docetaxel and prednisone in patients with mCRPC.

* Corresponding author. Department of Medicine, Division of Oncology, University of Washington and Fred Hutchinson Cancer Research Center, 825 Eastlake Avenue E, G4-830, Seattle, WA 98109-1023, USA. Tel. +1 206 6066292.
E-mail address: evanyu@u.washington.edu (E.Y. Yu).

https://doi.org/10.1016/j.eururo.2022.02.023

Keywords:
Docetaxel
Metastatic castration-resistant prostate cancer
Pembrolizumab
Prednisone

Design, setting, and participants: The trial included patients with mCRPC in the phase 1b/2 KEYNOTE-365 cohort B study who were chemotherapy naïve and who experienced failure of or were intolerant to ≥4 wk of abiraterone or enzalutamide for mCRPC with progressive disease within 6 mo of screening.
Intervention: Pembrolizumab 200 mg intravenously (IV) every 3 wk (Q3W), docetaxel 75 mg/m^2 IV Q3W, and prednisone 5 mg orally twice daily.
Outcome measurements and statistical analysis: The primary endpoints were safety, the prostate-specific antigen (PSA) response rate, and the objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) by blinded independent central review (BICR). Secondary endpoints included time to PSA progression; the disease control rate (DCR) and duration of response (DOR) according to RECIST v1.1 by BICR; ORR, DCR, DOR, and radiographic progression-free survival (rPFS) according to Prostate Cancer Working Group 3–modified RECIST v1.1 by BICR; and overall survival (OS).
Results and limitations: Among 104 treated patients, 52 had measurable disease. The median time from allocation to data cutoff (July 9, 2020) was 32.4 mo, during which 101 patients discontinued treatment, 81 (78%) for disease progression. The confirmed PSA response rate was 34% and the confirmed ORR (RECIST v1.1) was 23%. Median rPFS and OS were 8.5 mo and 20.2 mo, respectively. Treatment-related adverse events (TRAEs) occurred in 100 patients (96%). Grade 3–5 TRAEs occurred in 46 patients (44%). Seven AE-related deaths (6.7%) occurred (2 due to treatment-related pneumonitis). Limitations of the study include the single-arm design and small sample size.
Conclusions: Pembrolizumab plus docetaxel and prednisone demonstrated antitumor activity in chemotherapy-naïve naive patients with mCRPC treated with abiraterone or enzalutamide for mCRPC. Safety was consistent with profiles for the individual agents. Further investigation is warranted.
Patient summary: We evaluated the efficacy and safety of the anti-PD-1 antibody pembrolizumab combined with the chemotherapy drug docetaxel and the steroid prednisone for patients with metastatic prostate cancer resistant to androgen deprivation therapy, and who never received chemotherapy. The combination showed antitumor activity and manageable safety in this patient population.
This trial is registered on ClinicalTrials.gov as NCT02861573.

1. Introduction

Despite significant advances in the treatment of prostate cancer, the primary systemic treatment for regional or metastatic prostate cancer is androgen deprivation therapy (ADT) [1]. Most patients with metastatic disease develop resistance to ADT within 1–2 yr and progress to metastatic castration-resistant prostate cancer (mCRPC) [2]. Several treatment options show a survival benefit after development of mCRPC—including abiraterone [3], enzalutamide [4], docetaxel [5], cabazitaxel [6], sipuleucel-T [7], and radium-223 [8]—but are not curative. Next-generation hormonal agents (NHAs) such as abiraterone and enzalutamide are often used following disease progression after ADT, but there is no consensus regarding the optimal sequence for therapy after progression. Docetaxel is a recommended treatment after initial progression on abiraterone or enzalutamide despite the lack of prospective data for docetaxel after NHA therapy [1]. To date, docetaxel combination regimens have not shown a survival benefit over sequential monotherapies with docetaxel [1]. With a 5-yr survival rate estimated at 30% for patients with distant metastases [9,10], there is a need for therapies that prolong survival.

The tumor microenvironment is immunosuppressive in patients with prostate cancer, and therefore restoring the T-cell antitumor response via programmed death 1 (PD-1) or programmed death ligand 1 (PD-L1) blockade is a promising treatment approach [11,12]. Elevated expression of PD-L1 on tumor-infiltrating T cells has been associated with disease progression in prostate cancer [13]. Furthermore, a recent immunohistochemical study showed that metastases from CRPC tumors in patients previously treated with NHAs had increased PD-L1 expression and immunoreactivity [14]. Pembrolizumab is a highly selective humanized monoclonal antibody that blocks interaction between PD-1 and its ligands, PD-L1 and PD-L2, and is approved for the treatment of multiple tumor types [15]. In the phase 2 KEYNOTE-199 trial, pembrolizumab monotherapy showed antitumor activity with manageable safety in patients with mCRPC previously treated with docetaxel and one or more targeted endocrine therapies [16]. Preclinical studies have shown that many chemotherapeutic agents, including taxanes such as docetaxel, can have immunostimulatory effects [17]. Combining immunotherapy and standard chemotherapy may therefore enhance antitumor activity.

The phase 1b/2 KEYNOTE-365 trial (NCT02861573) evaluated the safety, tolerability, and efficacy of pembrolizumab combination therapy in patients with mCRPC. We describe the results for cohort B, which included chemotherapy-naïve patients with mCRPC who experienced disease progression

on abiraterone or enzalutamide for mCRPC and who were treated with the combination of pembrolizumab, docetaxel, and prednisone.

2. Patients and methods

2.1. Study design and patients

KEYNOTE-365 is a multicohort, nonrandomized, multicenter, open-label, phase 1b/2 trial. Patients in eight countries (Australia, Canada, France, Germany, New Zealand, Spain, UK, and USA) were enrolled in cohort B. The trial was conducted in accordance with good clinical practice and the Declaration of Helsinki. The protocol and its amendments were approved by the appropriate ethics body at each participating institution. All patients provided written informed consent.

Key eligibility criteria included age ≥18 yr; histologically or cytologically confirmed adenocarcinoma of the prostate without small-cell histology; disease that progressed within 6 mo before screening (prostate-specific antigen [PSA] progression or radiologic bone/soft tissue progression); Eastern Cooperative Oncology Group performance status score of 0 or 1; received ≥4 wk of treatment with either abiraterone or enzalutamide (but not both) for mCRPC and with treatment failure or intolerance to the drug; no previous chemotherapy; and serum testosterone level <50 ng/dL. The full inclusion and exclusion criteria are listed in the Supplementary material.

Pembrolizumab 200 mg was administered intravenously (IV) every 3 wk (Q3W) with docetaxel 75 mg/m^2 IV Q3W and prednisone 5 mg orally twice daily. Pembrolizumab was administered for up to 35 cycles (~2 yr), and docetaxel was administered for up to ten cycles.

2.2. Assessments and endpoints

On-study computed tomography or magnetic resonance imaging and radionuclide bone imaging were performed every 9 wk from the date of allocation through week 54, and then every 12 wk thereafter. The response and radiographic progression for soft tissue lesions were assessed according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), and radiographic progression for bone lesions was determined according to Prostate Cancer Working Group 3 (PCWG3)-modified RECIST v1.1. Imaging continued until confirmed disease progression, the start of a new anticancer treatment, withdrawal of consent, or death, whichever occurred first. PSA was assessed by a central laboratory at screening and every 3 wk after allocation. Follow-up time began at allocation. PD-L1 positivity was defined as a combined positive score (CPS) ≥1, where CPS is defined as the number of PD-L1–staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100.

Adverse events (AEs) were monitored throughout the study through 30 d after the last dose of trial treatment (90 d for serious AEs), graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Immune-mediated AEs were determined by the sponsor on the basis of a list of terms specified by the sponsor as potentially associated with immunologic causes.

Primary efficacy endpoints included the PSA response (PSA reduction of ≥50% from baseline, measured twice ≥3 wk apart) and the objective response rate (ORR; complete response [CR] or partial response [PR]) according to RECIST v1.1 as assessed by blinded independent central review (BICR). The primary safety objective was to characterize the safety and tolerability. Secondary endpoints included time to PSA progression; ORR according to PCWG3-modified RECIST v1.1 by BICR; the disease control rate (DCR; CR, PR, stable disease [SD] or non-CR/non-progressive disease [PD] ≥6 mo) and the duration of response (DOR) according to RECIST v1.1 and PCWG3-modified RECIST v1.1 by BICR; radiographic progression-free survival (rPFS) according to PCWG3-modified RECIST v1.1 by BICR; and overall survival (OS).

2.3. Statistical considerations

Efficacy and safety populations included all patients who received at least one dose of study treatment (all patients as treated [APaT]). APaT for ORR included only patients with measurable disease at baseline; APaT for DOR included only patients with an objective response. The Clopper-Pearson method was used to provide point estimates and 95% confidence intervals (CIs) for the PSA response rate, ORR, and DCR. The Kaplan-Meier method was used to provide median point estimates and 95% CIs for DOR, time to PSA progression, rPFS, and OS.

Safety and tolerability were assessed via clinical review of all relevant parameters, including AEs, laboratory tests, and vital signs. Counts and percentages for AEs are provided.

Table 1 – Patient demographics and baseline characteristics for the 104 patients treated with pembrolizumab + docetaxel + prednisone

Parameter	Result
Median age, yr (interquartile range)	68 (64–74)
Age ≥65 yr, *n* (%)	77 (74)
Race, *n* (%)	
White	79 (76)
All others	9 (8.7)
Unknown	16 (15)
Geographic region of enrolling site, *n* (%)	
North America	41 (39)
Europe	54 (52)
Rest of the world	9 (8.7)
Eastern Cooperative Oncology Group performance status, *n* (%)	
0	56 (54)
1	48 (46)
Median prostate-specific antigen, ng/mL (interquartile range)	44.1 (17.1–131.4)
PD-L1 status, *n* (%)	
Positive[a]	24 (23)
Negative	76 (73)
Unknown	4 (3.8)
Disease measurable according to RECIST v1.1, *n* (%)	52 (50)
Median baseline tumor size, mm (interquartile range) [b]	49.9 (26.9–73.8)
Visceral disease, *n* (%) [c]	
With liver	8 (7.7)
Without liver	18 (17)
No visceral disease	78 (75)
Metastatic staging, *n* (%)	
M1	61 (59)
M1A	4 (3.8)
M1B	34 (33)
M1C	5 (4.8)
History of brain metastases, *n* (%)	
No	101 (97)
Unknown	3 (2.9)
Previous use of abiraterone/enzalutamide, *n* (%)	
Abiraterone only	51 (49)
Enzalutamide only	52 (50)
Abiraterone and enzalutamide	1 (1.0)

RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.
[a] PD-L1 positivity was defined as a combined positive score (CPS) ≥1. CPS was calculated as the number of PD-L1–staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100.
[b] Assessed by blinded independent central review according to RECIST v1.1.
[c] Soft tissue (not in brain, bone, or lymph nodes).

3. Results

3.1. Disposition, demographics, and exposure

As of July 9, 2020, cohort B enrolled 105 patients; 104 patients whose median age was 68.0 yr (interquartile range [IQR] 64–74) with median PSA of 44.1 ng/mL (IQR 17.1–131.4) were treated (Table 1). Median time from allocation to data cutoff was 32.4 mo (IQR 12.2–27.8). At data cutoff, 101 patients (97%) had discontinued treatment (Supplementary Fig. 1). Among those patients, 81 (78%) discontinued because of disease progression and 15 (14%) because of AEs. Patients received a median of 12 cycles (IQR 7.5–15) of pembrolizumab, and 8.5 cycles (IQR 6–10) of docetaxel. All treated patients received at least two cycles of both treatments; 65 (63%) received at least ten cycles of pembrolizumab and 86 (83%) received at least six cycles of docetaxel. The median duration on therapy, defined as the time between the first dose date and the last dose date, was 7.7 mo (IQR 4.8–9.7).

3.2. Efficacy

The confirmed PSA response rate in patients with a baseline PSA measurement was 34% (35/103) for the total population and 27% (14/51) for patients with RECIST-measurable disease. Seventy-six patients (74%) exhibited any reduction in PSA from baseline, and 45 patients (44%) experienced a PSA reduction of ≥50% from baseline (Fig. 1A). Of 24 patients with PD-L1–positive tumors, 16 (67%) experienced a reduction in PSA from baseline and nine (38%) experienced a reduction of ≥50%. Overall, 56/75 patients (75%) with PD-L1–negative tumors experienced a reduction in PSA from baseline, whereas 35 patients (47%) experienced a reduction of ≥50%. The median time to PSA progression was 29.3 wk (95% CI 21–32; Fig. 1B). PSA response rates were generally consistent across subgroups (Supplementary Fig. 2A).

The confirmed ORR for patients with RECIST-measurable disease was 23% (CR, *n* = 0; PR, *n* = 12; Table 2). DCR was 54% for the total population by BICR according to RECIST v1.1. ORRs and DCRs were largely similar between subgroups (Supplementary Fig. 2B,C). Forty-seven of 52 patients (90%) experienced reductions in target lesion size from baseline, and 22 patients (42%) experienced reductions of >30% by BICR according to RECIST v1.1 (Fig. 2A). BICR assessment according to PCWG3-modified RECIST v1.1 revealed a DCR of 68% overall and a confirmed ORR of 33% for patients with measurable disease (Supplementary Table 1). For the 12 patients with a response, the estimated median DOR by BICR according to RECIST v1.1 was 6.3 mo (range 3.4–9.0+), and eight patients (67%) had a response duration ≥6 mo according to Kaplan-Meier estimates (Fig. 2B,C). BICR assessment according to PCWG3-modified RECIST v1.1 revealed a median DOR of 6.8 mo (range 3.4–10.4), and nine patients (62%) had a response duration ≥6 mo. Median rPFS was 8.5 mo (95% CI 8.3–10); the 6-mo rPFS rate was 77% and the 12-mo rPFS rate was 26% (Fig. 3A). Median OS was 20.2 mo (95% CI 17–24); the 6-mo OS rate was 96% and the 12-mo OS rate was 76% (Fig. 3B).

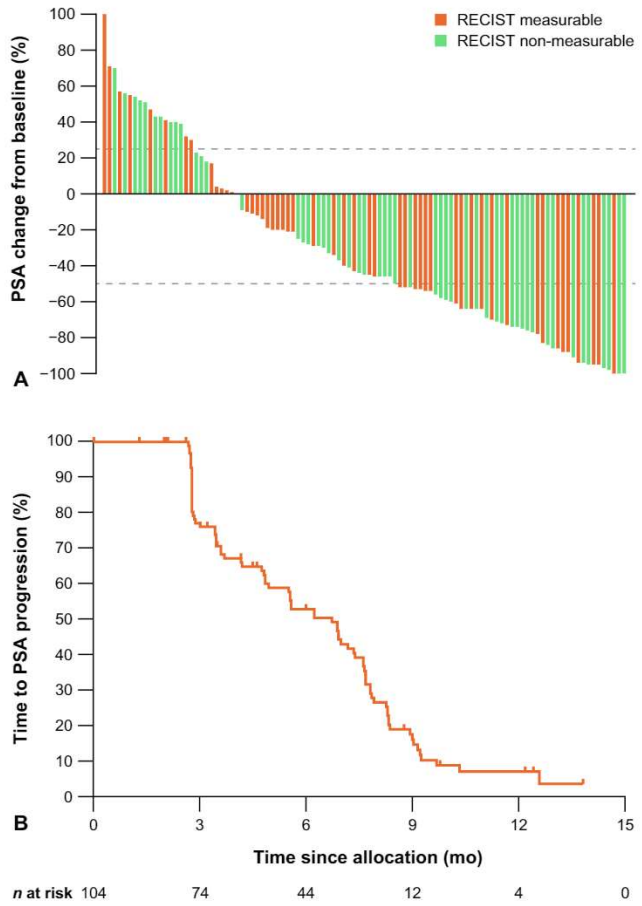


Fig. 1 – (A) Percentage PSA change from baseline (confirmed and unconfirmed; one patient did not have a baseline PSA measurement). (B) Kaplan-Meier estimate of time to PSA progression. PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumors.

3.3. Safety

Treatment-related AEs (TRAEs) attributed by the investigator occurred in 100 patients (96%) (Supplementary Table 2).

Table 2 – Confirmed best response by blinded independent central review according to RECIST v1.1

Parameter	RECIST-MD (*n* = 52)	RECIST-NMD (*n* = 52)	Total (*n* = 104)
Objective response rate, % (95% CI)	23 (13–37)	NA	NA
Disease control rate, % (95% CI) [a]	52 (38–66)	56 (41–70)	54 (44–64)
Best response, *n* (%)			
CR	0 (0)	NA	NA
PR	12 (23)	NA	NA
SD of any duration	26 (50)	0 (0)	26 (25)
Non-CR/non-PD	0 (0)	41 (79)	41 (39)
SD or non-CR/non-PD ≥6 mo	15 (29)	29 (56)	44 (42)
PD	14 (27)	11 (21)	25 (24)

CI = confidence interval; CR = complete response; MD = measurable disease; NA = not applicable; NMD = non-measurable disease; PD = progressive disease; PR = partial response; SD = stable disease; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.

[a] Disease control rate defined as CR + PR + SD or non-CR/non-PD ≥6 mo.

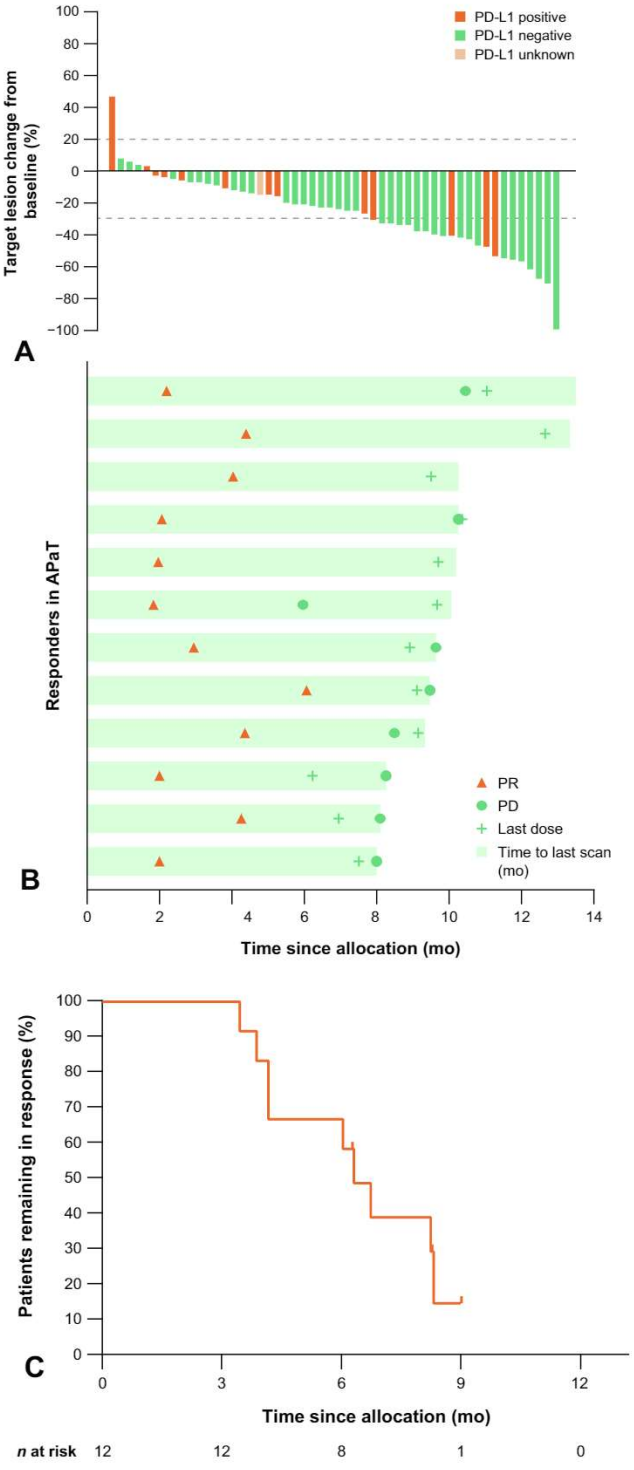


Fig. 2 – (A) Target lesion change from baseline (confirmed and unconfirmed), (B) time to response for responders by BICR according to RECIST version 1.1, and (C) Kaplan-Meier estimate of the duration of response for responders by BICR according to RECIST version 1.1. APaT = all patients as treated; BICR = blinded independent central review; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors.

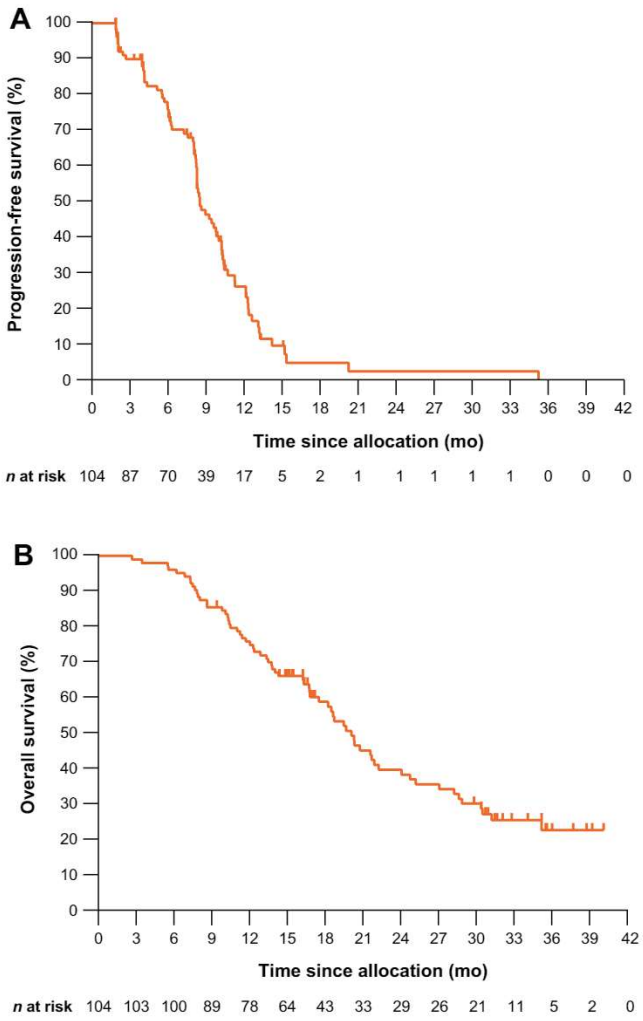


Fig. 3 – Kaplan-Meier estimates of (A) radiographic progression-free survival according to Prostate Cancer Working Group 3–modified Response Evaluation Criteria in Solid Tumors version 1.1 and (B) overall survival.

Grade 3–5 TRAEs occurred in 46 patients (44%). The most frequent TRAEs (incidence ≥20%) were diarrhea, fatigue, alopecia, dysgeusia, nausea, peripheral neuropathy, and asthenia (Table 3). The most frequent grade 3–5 TRAEs (incidence ≥2%) were febrile neutropenia, decreased neutrophil count, anemia, neutropenia, diarrhea, fatigue, pneumonitis, and decreased lymphocyte count. Serious TRAEs occurred in 24 patients (23%; Supplementary Table 3), and 28 (27%) discontinued because of TRAEs (pembrolizumab, *n* = 13 [13%]; docetaxel, *n* = 24 [23%]; prednisone, *n* = 10 [9.6%]).

Sponsor-defined immune-mediated AEs occurred in 34 patients (33%); nine (8.7%) experienced grade 3–5 events (pneumonitis, *n* = 4; colitis, *n* = 4; severe skin reaction, *n* = 1; Supplementary Table 4). The most common immune-mediated AEs (incidence ≥5%) were infusion reactions, hyperthyroidism, pneumonitis, colitis, and hypothyroidism. Of 46 immune-mediated AE episodes, ten (22%) necessitated concurrent systemic corticosteroids with a high starting dose (≥40 mg/d prednisone or equivalent).

Overall, seven patients (6.7%) died of AEs. Five deaths (4.8%) were unrelated to treatment (cerebrovascular accident, *n* = 1; pneumonia, *n* = 2; malignant neoplasm progression, *n* = 2). Two deaths (1.9%) from AEs (both pneumonitis, an immune-mediated AE) were related to treatment as

Table 3 – Treatment-related adverse events with ≥5% incidence among the 104 patients treated with pembrolizumab + docetaxel + prednisone

Treatment-related adverse event	Patients, *n* (%)	
	Any grade	Grade 3–5
Any	100 (96)	46 (44)
Diarrhea	43 (41)	3 (2.9)
Fatigue	43 (41)	3 (2.9)
Alopecia	42 (40)	0 (0)
Dysgeusia	28 (27)	0 (0)
Nausea	27 (26)	0 (0)
Peripheral neuropathy	23 (22)	0 (0)
Asthenia	22 (21)	2 (1.9)
Anemia	19 (18)	5 (4.8)
Decreased appetite	16 (15)	0 (0)
Peripheral edema	15 (14)	1 (1.0)
Mucosal inflammation	13 (13)	0 (0)
Febrile neutropenia	12 (12)	12 (12)
Dyspepsia	11 (11)	0 (0)
Paresthesia	11 (11)	0 (0)
Arthralgia	10 (9.6)	1 (1.0)
Dyspnea	10 (9.6)	0 (0)
Decreased neutrophil count	10 (9.6)	6 (5.8)
Peripheral sensory neuropathy	10 (9.6)	0 (0)
Hyperthyroidism	8 (7.7)	0 (0)
Nail discoloration	8 (7.7)	0 (0)
Nail disorder	8 (7.7)	0 (0)
Neutropenia	8 (7.7)	5 (4.8)
Pruritus	8 (7.7)	0 (0)
Pyrexia	8 (7.7)	0 (0)
Constipation	7 (6.7)	0 (0)
Cough	7 (6.7)	0 (0)
Dry skin	7 (6.7)	0 (0)
Infusion reaction	7 (6.7)	0 (0)
Insomnia	7 (6.7)	0 (0)
Pain in extremity	7 (6.7)	0 (0)
Pneumonitis	7 (6.7)	3 (2.9)
Exertional dyspnea	6 (5.8)	0 (0)
Flushing	6 (5.8)	0 (0)
Decreased lymphocyte count	6 (5.8)	3 (2.9)
Muscle spasms	6 (5.8)	0 (0)
Myalgia	6 (5.8)	0 (0)
Maculopapular rash	6 (5.8)	1 (1.0)

determined by the investigator. One death from pneumonitis occurred 40 d after the patient's last exposure to treatment (4 d after AE onset), and the other occurred 63 d after the patient's last exposure to treatment (13 d after AE onset).

4. Discussion

Combination therapy with pembrolizumab plus docetaxel and prednisone showed a clinical benefit for chemotherapy-naïve patients previously treated with abiraterone or enzalutamide for mCRPC in cohort B of the KEYNOTE-365 study. The confirmed PSA response rate was 34% for patients with baseline PSA measurements, with an ORR of 23% by BICR for those with measurable disease. Antitumor activity was noted in RECIST-measurable and bone-predominant disease, and in PD-L1–positive and PD-L1–negative tumors. The benefit was similar regardless of whether the previous NHA was abiraterone or enzalutamide. Among the patients with RECIST-measurable disease, none experienced CR, and 12 experienced PR as the best response. The target lesion size was reduced in 90% of patients in the current study, with 42% of patients experiencing reductions >30% by BICR. The safety profile of the combination was manageable and consistent with the profiles of the individual agents. The PSA response rate, ORR, and OS observed in the present study are higher than those observed in two cohorts of patients with RECIST-measurable mCRPC in the phase 2 KEYNOTE-199 study of pembrolizumab monotherapy (cohort 1 [PD-L1–positive]: PSA response, 6%; ORR, 6%; OS, 9.5 mo; cohort 2 [PD-L1–negative]: PSA response, 8%; ORR, 3%; OS, 7.9 mo) [18]. However, patients in KEYNOTE-199 previously received docetaxel, whereas patients in KEYNOTE-365 cohort B had chemotherapy-naïve mCRPC.

The efficacy of docetaxel was established in the phase 3 study of docetaxel and prednisone versus mitoxantrone and prednisone in patients with mCRPC who experienced progression during hormone therapy and subsequently received antiandrogen therapy [19]. Docetaxel Q3W led to a 2.4-mo improvement in OS versus mitoxantrone (18.9 vs 16.5 mo; hazard ratio [HR] 0.76, 95% CI 0.62–0.94; p = 0.009). Confirmed PSA levels decreased by ≥50% from baseline in 45% of patients receiving docetaxel and 32% receiving mitoxantrone. In the current study, the confirmed PSA response rate was 34%. The docetaxel versus mitoxantrone study took place before the development of abiraterone and enzalutamide; hence, the data are limited regarding the efficacy of docetaxel after NHA treatment, and the optimal order of therapies is not clear.

The phase 3 FIRSTANA trial compared OS after cabazitaxel (two dose schedules) versus docetaxel in 1168 patients with chemotherapy-naïve mCRPC [20]. For the docetaxel group, the median OS was 24.3 mo, the median time to tumor progression was 12.1 mo, and the tumor response rate (CR or PR) was 31%. However, few patients enrolled in FIRSTANA had previously received enzalutamide or abiraterone. In one retrospective study that included patients from a phase 1/2 abiraterone trial, median OS for patients who received docetaxel after abiraterone was 12.5 mo (95% CI 10.6–19.4), and 13 patients (37%) experienced a PSA decrease of ≥30% [21]. By contrast, the current study showed longer OS after pembrolizumab plus docetaxel and prednisone (20.2 mo, 95% CI 16.9–24.2) than previously reported. Cross-resistance between abiraterone and docetaxel could be the reason why patients receiving docetaxel after abiraterone are more likely to experience disease progression, but additional studies are needed to confirm this hypothesis [21,22]. Enzalutamide has also been used in patients with mCRPC with disease progression after abiraterone. Although the sample size was small (n = 61), a retrospective analysis compared docetaxel (n = 31) and enzalutamide (n = 30) in patients with mCRPC whose disease had progressed on abiraterone [23]. In a multivariable logistic model controlled for baseline and primary refractoriness to previous abiraterone therapy, there was no significant difference between the groups in the odds of a PSA decline of ≥30% (odds ratio 2.17, 95% CI 0.68–7.30; p = 0.20) or ≥50% (odds ratio 1.68, 95% CI 0.51–5.66; p = 0.40). Median PSA PFS was 4.1 mo for both the docetaxel and enzalutamide cohorts (HR 1.35, 95% CI 0.53–3.656); median PFS was 4.7 mo for the enzalutamide cohort and 4.4 mo for the docetaxel cohort (HR, 1.44, 95% CI 0.77–2.71; p = 0.257) [23]. A mouse model of CRPC showed lower

efficacy of docetaxel in mice with enzalutamide-resistant tumors compared with enzalutamide-naïve tumors, similar to the hypothesized cross-resistance between abiraterone and docetaxel [24]. These findings suggest that further study of the optimal sequencing of NHA and chemotherapy agents such as docetaxel may be warranted.

The current study is limited by its small sample size and single-arm design. However, the promising ORR (23%; n = 12 with PR) and OS (20.2 mo) served as a rationale to further investigate this treatment combination in KEYNOTE-921 (NCT03834506). KEYNOTE-921 is a randomized, global, parallel-group, double-blind, phase 3 trial to investigate pembrolizumab (200 mg IV Q3W) plus docetaxel (75 mg/m^2 IV Q3W) and prednisone (5 mg orally twice daily) versus placebo plus docetaxel and prednisone in patients with histologically or cytologically confirmed chemotherapy-naïve mCRPC with disease progression after NHA therapy [25].

The phase 2 CheckMate 9KD study examined the PD-L1 inhibitor nivolumab combined with docetaxel and prednisone. The ORR was 36.8%, with median rPFS of 8.2 mo after minimum follow-up of 28 wk for patients with chemotherapy-naïve mCRPC (65% previously received abiraterone or enzalutamide), similar to the rPFS in the current study (8.5 mo) with comparable safety results [26]. The subsequent phase 3 CheckMate 7DX trial will further investigate this combination.

Mismatch repair deficiency (dMMR), microsatellite instability, and/or hypermutation are believed to be potential enrichment biomarkers for response to immunotherapy in patients with solid tumor malignancies. However, the microsatellite instability-high/dMMR phenotype is rare in mCRPC, affecting only 3–4% of patients [27,28]. There is limited information about and there are no trial data for the response rate to pembrolizumab for this rare prostate cancer population. Therefore, we feel it is unlikely that our findings were significantly affected by these potential enrichment factors.

5. Conclusions

Pembrolizumab plus docetaxel and prednisone demonstrated antitumor activity in chemotherapy-naïve patients with mCRPC previously treated with abiraterone or enzalutamide for mCRPC. OS was longer than observed in previous studies in this population, and the ORR is similarly promising. The safety profile was manageable and consistent with the known profiles of each agent. Our results show activity for this combination, which will be confirmed in the phase 3 KEYNOTE-921 trial.

Author contributions: Evan Y. Yu had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: de Bono, Yu, Poehlein, Schloss.
Acquisition of data: Appleman, Berry, Bögemann, Conter, de Bono, Emmenegger, Yu, Gravis, Gurney, Joshua, Kolinsky, Laguerre, Linch, Massard, Mourey, Piulats, Poehlein, Romano, Schloss, Sridhar.
Analysis and interpretation of data: Appleman, Bögemann, Conter, de Bono, Yu, Gurney, Joshua, Kolinsky, Laguerre, Li, Linch, Retz, Massard, Piulats, Poehlein, Romano, Schloss, Sridhar.
Drafting of the manuscript: Bögemann, de Bono, Yu, Joshua, Laguerre, Poehlein, Schloss.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: None.
Obtaining funding: Massard.
Administrative, technical, or material support: Retz, Massard, Schloss.
Supervision: None.
Other (*provision of study materials/patients*): Appleman, Berry, de Bono, Emmenegger, Yu, Gravis, Gurney, Joshua, Linch, Massard, Mourey, Piulats.

Financial disclosures: Evan Y. Yu certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Evan Y. Yu has received personal fees from Bayer, Clovis, Janssen, Merck, SeaGen, Sanofi, AbbVie, Advanced Accelerator Applications, and Exelixis, and has received grants from SeaGen, Daiichi-Sankyo, Taiho, Blue Earth, and Lantheus. Michael P. Kolinsky has received personal consultancy fees from Astellas, AstraZeneca, Bayer, BMS, Eisai, Ipsen, Janssen, and Merck. William R. Berry has received personal advisory fees from Merck. Margitta Retz has nothing to disclose. Loic Mourey has received personal fees and nonfinancial support from Sanofi, Astellas, Janssen, Ipsen, AstraZeneca, Pfizer, BMS, and MSD. Josep M. Piulats has received research grants and personal fees from MSD. Leonard J. Appleman has received personal consultancy fees from AADi; has received institutional grants from Astellas Pharma, Amgen, AVEO, Bayer, BMS, Eisai, Epizyme, Exelexis, Genentech/Roche, Inovio Pharmaceuticals, Lilly, Merck, Novartis, Peleton Therapeutics, Pfizer, Surface Oncology, and Tokai; and has received institutional research contracts from Bayer, Calithera Biosciences, Seattle Genetics, and BioNTech. Emanuela Romano has nothing to disclose. Gwenaelle Gravis has received institutional research grants from Janssen, Astellas, MSD, BMS, Pfizer, Alliance Merck-Pfizer, Amgen, Sanofi, and AAA; has received personal speaker fees from Janssen, Astellas, BMS, MSD, Amgen, and Sanofi; and has received personal advisory fees from Janssen, Astellas, BMS, Pfizer, Alliance Merck-Pfizer, and AAA. Howard Gurney has received personal speaker fees from MSD and personal advisory fees from MSD, Roche, Merck, BMS, Pfizer, and Ipsen. Martin Bögemann has received personal fees from MSD, Janssen, Bayer, and Sanofi and has received a grant from Janssen. Urban Emmenegger has received personal advisory fees from Amgen, Astellas, AstraZeneca, Bayer, Ferring, Janssen, Merck, and Knight; has received institutional research grants from Astellas, AstraZeneca, Bayer, Endocyte (Novartis), Janssen, Merck, and Roche/Genentech; and has received personal research grants from Astellas, Bayer, and Janssen. Anthony M. Joshua has received institutional grants from Merck and Sanofi. Mark Linch has nothing to disclose. Srikala Sridhar has received grants from Pfizer, Bayer, and AstraZeneca; and has received personal fees from Astellas, Janssen, and Immunomedics. Henry J. Conter has received personal fees from Hoffmann La-Roche Canada. Brigitte Laguerre has received honoraria from MSD, BMS, AstraZeneca, Ipsen, and Roche; and has received personal speaker fees from Astellas, Janssen, and Pfizer. Christophe Massard has received personal consultancy fees from Amgen, Astellas, AstraZeneca, Bayer, BeiGene, BMS, Celgene, Debiopharm, Genentech, Ipsen, Janssen, Lilly, MedImmune, MSD, Novartis, Pfizer, Roche, Sanofi, and Orion; and has served as a principal investigator or subinvestigator of clinical trials for AbbVie, Aduro, Agios, Amgen, Argenx,

Astex, AstraZeneca, Aveo Pharmaceuticals, Bayer, BeiGene, Blueprint, BMS, Boehringer Ingelheim, Celgene, Chugai, Clovis, Daiichi Sankyo, Debiopharm, Eisai, Eos, Exelixis, Forma, GamaMabs, Genentech, Gortec, GSK, H3 Biomedicine, Incyte, Innate Pharma, Janssen, Kura Oncology, Kyowa, Lilly, Loxo, Lysarc, Lytix Biopharma, MedImmune, Menarini, Merus, MSD, Nanobiotix, Nektar Therapeutics, Novartis, Octimet, OncoEthix, Oncopeptides AB, Orion, Pfizer, PharmaMar, Pierre Fabre, Roche, Sanofi, Servier, Sierra Oncology, Taiho, Takeda, Tesaro, and Xencor. Xin Tong Li is an employee of MSD China. Charles Schloss and Christian H. Poehlein are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and own stock in Merck & Co., Inc., Kenilworth, NJ, USA. Johann S. de Bono has received personal fees and travel expenses for serving as an advisor for Amgen, Astellas, AstraZeneca, Bayer, BioXcel Therapeutics, Boehringer Ingelheim, CellCentric, Daiichi, Eisai, Roche/Genentech, Genmab, GlaxoSmithKline, Harpoon, Janssen, Menarini Silicon Biosystems, Merck Serono, Merck Sharp & Dohme, Orion Pharma, Pfizer, Qiagen, Sanofi Aventis, Sierra Oncology, Taiho, Terumo, and Vertex Pharmaceuticals; has received institutional grants from Astellas, AstraZeneca, Bayer, CellCentric, Daiichi, Roche/Genentech, Genmab, GlaxoSmithKline, Harpoon, Janssen, Merck Serono, Merck Sharp & Dohme, Orion Pharma, Pfizer, Sanofi Aventis, Sierra Oncology, Taiho, and Vertex Pharmaceuticals; and holds patents WO 2005 053662 licensed to AstraZeneca and US5604213 licensed to Janssen, for which he receives no personal income.

***Funding/Support and role of the sponsor*:** Funding for this research was provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. The sponsor played a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, and approval of the manuscript. Evan Y. Yu was also supported in part by the Department of Defense Prostate Cancer Clinical Trials Consortium grant W81XWH-16-PCRP-CCRSA.

Acknowledgments: The data used in this manuscript were presented in part at the American Society of Clinical Oncology 2021 Genitourinary Cancers (ASCO-GU) Virtual Symposium, February 11–13, 2021. Previous iterations of the study using earlier database cutoff dates were presented in part at the European Society for Medical Oncology (ESMO) Asia Virtual Meeting, November 20–22, 2020; the European Society of Urology Virtual Congress, July 17–21, 2020; the ESMO 2020 Virtual Congress, September 19–21, 2020; the ASCO 2020 Virtual Congress, May 29–31, 2020; the ASCO-GU Symposium, February 13–15, 2020; the ASCO 2019 Annual Meeting, May 31–June 4, 2019; and the ASCO-GU 2019 Meeting, February 14–16, 2019. We thank the patients and their families and caregivers for participating in the study. Michelle Carbuto and Adi Avidar, both from Merck & Co., Inc., Kenilworth, NJ, USA, under contract with ExecuPharm, provided study support. Medical writing and/or editorial assistance was provided by Shane Walton, PhD, and Matthew Grzywacz, PhD, of ApotheCom (Yardley, PA, USA). This assistance was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Data sharing statement: Merck Sharp & Dohme Corp. (MSD), a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data sharing website (available at: http://engagezone.msd.com/ds_documentation.php) outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with MSD before data access is granted. Data will be made available for request after product approval in the US and EU or after product development is discontinued. There are circumstances that may prevent MSD from sharing requested data, including country or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, MSD will either perform the proposed analyses and share the results with the requestor or will construct biomarker covariates and add them to a file with clinical data that is uploaded to an analysis portal so that the requestor can perform the proposed analyses.

Appendix A. Supplementary data

Peer Review Summary and Supplementary Data associated with this article can be found online at https://doi.org/10.1016/j.eururo.2022.02.023.

References

[1] National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Prostate cancer v2.2021. Plymouth Meeting, PA: National Comprehensive Cancer Network; 2021.
[2] Fizazi K, Tran N, Fein L, et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med 2017;377:352–60.
[3] Fizazi K, Scher HI, Molina A, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 2012;13:983–92.
[4] Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012;367:1187–97.
[5] Berthold DR, Pond GR, Soban F, de Wit R, Eisenberger M, Tannock IF. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. J Clin Oncol 2008;26:242–5.
[6] de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 2010;376:1147–54.
[7] Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411–22.
[8] Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med 2013;369:213–23.
[9] Francini E, Gray KP, Shaw GK, et al. Impact of new systemic therapies on overall survival of patients with metastatic castration-resistant prostate cancer in a hospital-based registry. Prostate Cancer Prostat Dis 2019;22:420–7.
[10] Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. CA Cancer J Clin 2021;71:7–33.
[11] Pasero C, Gravis G, Guerin M, et al. Inherent and tumor-driven immune tolerance in the prostate microenvironment impairs natural killer cell antitumor activity. Cancer Res 2016;76:2153–65.
[12] Boettcher AN, Usman A, Morgans A, VanderWeele DJ, Sosman J, Wu JD. Past, current, and future of immunotherapies for prostate cancer. Front Oncol 2019;9:884.

[13] Gevensleben H, Dietrich D, Golletz C, et al. The immune checkpoint regulator PD-L1 is highly expressed in aggressive primary prostate cancer. Clin Cancer Res 2016;22:1969–77.
[14] Haffner MC, Guner G, Taheri D, et al. Comprehensive evaluation of programmed death-ligand 1 expression in primary and metastatic prostate cancer. Am J Pathol 2018;188:1478–85.
[15] KEYTRUDA® (pembrolizumab) injection, for intravenous use. Whitehouse Station, NJ: Merck Sharp & Dohme Corp; 2021.
[16] Antonarakis ES, Piulats JM, Gross-Goupil M, et al. Pembrolizumab for treatment-refractory metastatic castration-resistant prostate cancer: multicohort, open-label phase II KEYNOTE-199 study. J Clin Oncol 2020;38:395–405.
[17] Heinhuis KM, Ros W, Kok M, Steeghs N, Beijnen JH, Schellens JHM. Enhancing antitumor response by combining immune checkpoint inhibitors with chemotherapy in solid tumors. Ann Oncol 2019;30:219–35.
[18] Antonarakis ES, Piulats JM, Gross-Goupil M, et al. 611P Pembrolizumab (pembro) monotherapy for docetaxel-pretreated metastatic castration-resistant prostate cancer (mCRPC): updated analyses with 4 years of follow-up from cohorts 1–3 of the KEYNOTE-199 study. Ann Oncol 2021;32(Suppl 5):S651–2.
[19] Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004;351:1502–12.
[20] Oudard S, Fizazi K, Sengelov L, et al. Cabazitaxel versus docetaxel as first-line therapy for patients with metastatic castration-resistant prostate cancer: a randomized phase III trial—FIRSTANA. J Clin Oncol 2017;35:3189–97.
[21] Mezynski J, Pezaro C, Bianchini D, et al. Antitumour activity of docetaxel following treatment with the CYP17A1 inhibitor abiraterone: clinical evidence for cross-resistance? Ann Oncol 2012;23:2943–7.
[22] Schweizer MT, Zhou XC, Wang H, et al. The influence of prior abiraterone treatment on the clinical activity of docetaxel in men with metastatic castration-resistant prostate cancer. Eur Urol 2014;66:646–52.
[23] Suzman DL, Luber B, Schweizer MT, Nadal R, Antonarakis ES. Clinical activity of enzalutamide versus docetaxel in men with castration-resistant prostate cancer progressing after abiraterone. Prostate 2014;74:1278–85.
[24] van Soest RJ, de Morrée ES, Kweldam CF, et al. Targeting the androgen receptor confers in vivo cross-resistance between enzalutamide and docetaxel, but not cabazitaxel, in castration-resistant prostate cancer. Eur Urol 2015;67:981–5.
[25] Petrylak DP, Ratta R, Gafanov R, et al. KEYNOTE-921: phase III study of pembrolizumab plus docetaxel for metastatic castration-resistant prostate cancer. Future Oncol 2021;17:3291–9.
[26] Fizazi K, Gonzalez Mella P, Castellano D, et al. Efficacy and safety of nivolumab in combination with docetaxel in men with metastatic castration-resistant prostate cancer in CheckMate 9KD. Ann Oncol 2019;30(Suppl 5):1612.
[27] Abida W, Cheng ML, Armenia J, et al. Analysis of the prevalence of microsatellite instability in prostate cancer and response to immune checkpoint blockade. JAMA Oncol 2019;5:471–8.
[28] Antonarakis ES, Piulats Rodriguez JMM, Gross-Goupil M, et al. Biomarker analysis from the KEYNOTE-199 trial of pembrolizumab in patients (pts) with docetaxel-refractory metastatic castration-resistant prostate cancer (mCRPC). J Clin Oncol 2020;38(Suppl 15):5526.

Appendix 3

Curricula vitae:

Heather H. Cheng – PI [2020-2022]

Evan Y. Yu - co-investigator

Michael T. Schweizer - co-investigator

Celestia Higano – PI [2017-2020]

UNIVERSITY OF WASHINGTON
SCHOOL OF MEDICINE

January 8, 2023

CURRICULUM VITAE

HEATHER H. CHENG, MD, PhD

1. Personal Data:

Place of birth:
Citizenship:

2. Education:

1994-1998	Bachelor of Arts, Molecular Biology Princeton University, Princeton, NJ
2000-2005	Doctor of Philosophy, Molecular and Cellular Biology University of Washington, Seattle, WA
1998-2007	Doctor of Medicine (NIH Medical Scientist Training Program) University of Washington School of Medicine, Seattle, WA

3. Postgraduate Training:

06/2007-06/2009	Internship and Residency, Internal Medicine University of Washington, Seattle, WA
07/2009-08/2014	Fellowship, Hematology-Oncology (ABIM Research Pathway) University of Washington, Seattle, WA

4. Faculty Positions Held:

03/2014-06/2019	Assistant Professor, Division of Medical Oncology, Department of Medicine, University of Washington, Seattle, WA
03/2014-06/2019	Assistant Professor, Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA
07/2019-present	Associate Professor, Division of Medical Oncology, Department of Medicine University of Washington, Seattle, WA
07/2019-present	Associate Professor, Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA
04/2021-present	Adjunct Associate Professor, Department of Laboratory Medicine and Pathology, University of Washington, Seattle, WA

5. Hospital Positions Held:

03/2014-present	Attending Physician, Genitourinary Medical Oncology Clinics Seattle Cancer Care Alliance, Seattle, WA
03/2014-present	Attending Physician, Inpatient Oncology Service, Oncology Consult Service, University of Washington Medical Center, Seattle, WA
09/2016-present	Director, Prostate Cancer Genetics Clinic Seattle Cancer Care Alliance, Seattle, WA
02/2019-present	Attending Physician, Genitourinary Cancer Risk Management (GU/GICP) Seattle Cancer Care Alliance, Seattle, WA

6. Current (non-UW) Employment: n/a

7. Honors:

1998 Sigma Xi Society, Princeton, NJ
1998 New Jersey Cancer Commission Research Fellowship
2000 Paul Allen Research Fellowship
2009 University of Washington School of Medicine: Resident Teaching Award
2012 American Society of Clinical Oncology/National Cancer Institute Markers in Cancer Meeting, Merit Award
2014 American Society of Clinical Oncology Genitourinary Oncology Symposium, Merit Award
2014 American Society of Clinical Oncology Annual Meeting, Merit Award
2015 Prostate Cancer Foundation Young Investigator Award
2015 SWOG Integrated Translational Science Workshop, Cold Spring Harbor
2017 Becker's Healthcare, Rising Stars: Healthcare Leaders Under 40
2020 National Cancer Institute, Cancer Clinical Investigator Team Leadership Award

8. Board Certification:

2010 American Board of Internal Medicine, Certification in Internal Medicine
2013 American Board of Internal Medicine, Certification in Medical Oncology

9. Current License(s) to Practice:

Washington State Medical License #MD60095549 expires 11/03/2024
DEA #FC2472328 expires 08/31/2025

10. Diversity, Equity and Inclusion Activities:

2020-present Prostate Cancer Clinical Trials Consortium Diversity and Outreach Committee
2022 Ad hoc mentor for Fred Hutchinson Cancer Center Eddie Méndez Scholar Awardee, Aileen Fernandez PhD, post-doctoral fellow, Yale University
2022-present Career advisor for Morehouse School of Medicine/University Washington Medical Scientist Training Program student, Gygeria Manuel

11. Professional Organizations:

2022-present American Urological Association
2009-present American Society of Clinical Oncology
2005-present American Association of Cancer Research
2013-present Southwest Oncology Group (SWOG)
2005-2009 American College of Physicians
1998-2009 Physicians for Social Responsibility

12. Teaching Responsibilities:

2020-present **Associate Program Director, University of Washington/Fred Hutchinson Cancer Center Medical Scientist Training Program**

COURSES: University of Washington School of Medicine:
2012-2013 ***HUBIO 513, 522 and 535****, Intro to Clinical Medicine,* Small Group Leader
2014 ***MEDECK 614****, Medical Oncology Clerkship*, Richard Stein, MS4 (Fall 2014).
2014 ***HUBIO 550***, *Introduction to Clinical Medicine*, panelist
2014-2016 ***MED 505****, Dept of Medicine Preceptorship,* clinical preceptor: Dilip Nagakar, MS1 (Fall 2014); Caroline Jackson, MS1 (Fall 2015); J.D. Neumeister, MS2 (Fall 2016)
2016-2017 ***MEDSCI 540A****, Blood and Cancer*, small group leader

TEACHING/COMMITTEES:
A. Residents, Graduate Students & Medical Students (*primary mentor)
2017 Paul Katangole, MD, MS, (Uganda Cancer Institute), mentor for NCI Fogarty International Center Fellow Candidate

2018-2019	***Darren Pouv, 1st year medical student,** University of Washington School of Medicine, primary research mentor, Independent Investigative Inquiry
2020	Emiko M. Oshima, University of Washington School of Medicine: MPH candidate, research mentoring committee member
2022	Sunny Ren, University of Washington Genetic Counseling Program, Masters candidate, research project co-mentor

B. Subspecialty Fellows (*primary/co-primary mentor)

2014-2015	Faculty advisor for UW/FHCRC Heme/Onc Fellows' Solid Tumor Conference
2014-present	Teaching Faculty for Heme/Onc fellows and Internal Medicine residents in Genitourinary Oncology and Bladder Multi-disciplinary Clinics and Inpatient Oncology service.
2018-2021	***Alexandra Sokolova, MD,** University of Washington/Fred Hutch Heme/Onc fellow, primary research mentor, current position: Assistant Professor at Oregon Health Sciences University (as of 2022)
2019-present	Faculty Champion for Hematology/Oncology Fellowship, Outpatient Genitourinary Oncology Block
2019-2022	**Risa Wong, MD,** University of Washington/Fred Hutch Heme/Onc fellow, research co-mentor, current position: Assistant Professor at University of Pittsburg
2021-present	***Hiba Khan, MD, MPH,** University of Washington/Fred Hutch Hematology/Oncology fellow, primary research co-mentor
2022-present	**Ruben Raychaudry, MD,** University of Washington/Fred Hutch Hematology/Oncology fellow, research project co-mentor

13. Editorial Responsibilities: n/a

14. Special National Responsibilities:

June 2017	Organizing Chair, Coffey-Holden Prostate Cancer Academy*, Carlsbad, CA (*prestigious invitation-only annual meeting for ~75 prostate cancer researchers)
June 2017-	**Chair, Prostate Cancer Clinical Trials Consortium/PCF Genetics Working Group**
2017-2018	Co-Leader, Prostate Cancer Foundation DNA Repair Working Group
October 2017	Session Chair, DNA Repair, Prostate Cancer Foundation 24th Scientific Retreat, Washington D.C.
February 2018	Prostate Cancer Foundation Delegation on Prostate Cancer Genetics, Tel Aviv, Israel
April 2018-	Healthcare and Scientific Advisory Board, FORCE: Facing Hereditary Cancer Empowered Organization
June 2018	Education Session Chair, American Society for Clinical Oncology, 2018 Annual Meeting, Practical Methods for Integrating Genetic Testing into Clinical Practice for Advanced Prostate Cancer, Chicago, IL
August 2019-	Member, **Prostate Cancer Guidelines Panel, National Comprehensive Cancer Network, (NCCN)**
2020-2021	Board of Directors, Us-TOO International Prostate Cancer Education and Support Network (private, non-profit 501(c)3)
October 2020-	**Member, Prostate Cancer Task Force, National Cancer Institute Genitourinary Steering Committee**
June 2021-	**Member, American Society for Clinical Oncology, Annual Meeting Education Committee**: Genitourinary Cancer—Prostate, Testicular, and Penile Track (3-year term)
August 2021-	Member, Germline and Somatic Genomic Testing for Advanced and Metastatic Prostate Cancer Guideline Panel, American Society for Clinical Oncology
March 2022-	Member, American Urological Association Salvage Therapy for Prostate Cancer Panel
May 2022-	Member, Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic Panel **Guidelines Panel, National Comprehensive Cancer Network, (NCCN)**
Oct 2022-	**Chief Scientific Officer, BRCA Research & Cure Alliance (CureBRCA)**

June 2023 Education Session Chair, American Society for Clinical Oncology, 2023 Annual Meeting, Genetic and Genomic Testing for Prostate Cancer: Beyond DNA Repair Deficiencies, Chicago, IL

15. Special Local Responsibilities:

2011	University of Washington Hematology-Oncology Fellowship, fellow representative
2010-2011	University of Washington Hematology-Oncology Fellows Orientation Handbook, first editor and author
2011-2012	University of Washington Hematology-Oncology Solid Tumor Conference, fellow organizer
2014-2019	Genitourinary Cancer Clinical Research Database, faculty lead
2015-2016	Seattle Cancer Care Alliance Schwartz Center Rounds Planning Committee
2016-present	**Fred Hutchinson Cancer Center/University of Washington Cancer Consortium Data Safety Monitoring Committee**
2018-2021	Fred Hutch/Clinical Research Division, Appointments and Promotions Committee
2019-2020	Fred Hutch/Human Biology Division, Prostate Program Faculty Search Committee
2021	Fred Hutch/UW Cancer Consortium Pilot Award Review Committee
2020-2021	SCCA Genitourinary Medical Oncology Community Research Working Group lead
2022-present	Faculty search committee for University of Washington, Department of Urology

16. Research Funding

CURRENT RESEARCH SUPPORT

Title: 2021 Prostate Cancer Clinical Consortium Clinical Research Site: University of Washington
Major Goals: The proposed study will 1) characterize advanced prostate cancer using new genotypic and phenotypic methods and inform the design of precision oncology clinical trials, 2) define and address mechanisms of therapeutic resistance by developing clinical trials of novel therapeutic combinations, and 3) advance equitable delivery of precision oncology clinical trials to men with prostate cancer from high-risk, underserved and/or military populations.
Status of Support: Active
Project Number: W81XWH-22-2-0016
Name of PD/PI: Heather Cheng
Source of Support: US Department of Defense (DOD)
Primary Place of Performance: Fred Hutch Cancer Center – Seattle, WA
Project/Proposal Start and End Date: 09/30/2022 – 09/29/2026
Total Award Amount:

Title: Pacific Northwest (PNW) Prostate Cancer Sponsored Program of Research Excellence (SPORE) Project 1: Molecular Predictors of Prostate Cancer Progression and Mortality
Major Goals: The proposed study will ascertain and recruit germline cancer risk mutation carriers from: 1) population- and clinic-based incident cases of metastatic PC to find index cases with germline cancer risk mutations; 2) to conduct a PC early detection study incorporating novel biomarkers for unaffected, male germline mutation carriers (including first degree relatives of those with metastatic PC who are mutation carriers); and 3) to understand the cascade genetic testing process what will facilitate an innovative recruitment strategy for recruiting men at highest genetic risk of aggressive prostate cancer.
Status of Support: Active
Project Number: 5 P50 CA097186-16
Name of PD/PI: Peter Nelson
Source of Support: NIH/NCI
Primary Place of Performance: Fred Hutch Cancer Center – Seattle, WA
Project/Proposal Start and End Date: 09/01/18 to 08/31/23
Total Award Amount:

Title: 2020 Cancer Clinical Investigator Team Leadership Award (CCITLA)
Major Goals: To work with cancer consortium staff and colleagues to harmonize genitourinary cancer clinical trial portfolio and transfer to media-friendly formats. To expand cancer genetics care delivery to newer formats to expand delivery of care and disseminate research opportunities to the cancer center catchment and region.
Status of Support: Active
Project Number: CCITLA - Yr 4 2023
Name of PD/PI: Heather Cheng
Source of Support: Fred Hutchinson Cancer Center
Primary Place of Performance: Fred Hutchinson Cancer Center – Seattle, WA
Project/Proposal Start and End Date: 01/01/2020 – 12/31/2023
Total Award Amount:

Title: ACT PROMISE (Cheng)
Major Goals: The major goal of this study, in collaboration with Dr. Channing Paller, is to design, implement, recruit patients, and identify prostate cancer patients who carry germline pathogenic variants, assessing frequency, family history, outcomes, longitudinal treatment response, treatment sequences and therapy combinations.
Status of Support: Active
Project Number: ACT c19-235-Promise Registry
Name of PD/PI: Heather Cheng
Source of Support: DOD PROSTATE CANCER CLINICAL TRIALS CONSORTIUM
Primary Place of Performance: Fred Hutch Cancer Center – Seattle, WA
Project/Proposal Start and End Date: 06/19/2020 to 06/30/2024
Total Award Amount:

Title: PLATI-PARP: A phase 2 study of induction docetaxel and carboplatin followed by maintenance rucaparib in treatment of patients with metastatic castration resistant prostate cancer with homologous recombination DNA repair deficiency
Status of Support: Active
Project Number: 338-IIT-071
Name of PD/PI: Heather Cheng
Source of Support: Clovis Oncology, Inc
Primary Place of Performance: Fred Hutch Cancer Center – Seattle, WA
Project/Proposal Start and End Date: 07/26/2018 to 08/30/2023
Total Award Amount:

Title: Enhanced Genetic Awareness and Genetic Evaluation for Men Through Technology - The ENGAGEMENT Study
Major Goals: The project will 1) Develop and implement a web-based virtual PCA genetics board across academic, community, and VA settings. Perceived usefulness, acceptability, self-efficacy for genetically-based recommendations, and genetics knowledge from dynamic case-based learning will be assessed. 2) Establish a web-based, national, patient-driven registry for any male who has undergone PCA genetic testing to assess men's experience with the genetic evaluation process and inform patient centered genetics practice and resource development. 3) Utilize digital media to share updated information on genetic testing and precision management of PCA through a public-facing podcast series.
Status of Support: Active
Project Number: W81XWH2010310
Name of PD/PI: Veda Giri
Source of Support: US Department of Defense (DOD)
Primary Place of Performance: Fred Hutch Cancer Center – Seattle, WA
Project/Proposal Start and End Date: 09/30/2020-09/29/2023
Total Award Amount:

Title: A Study of Rucaparib Versus Physician's Choice of Therapy in Patients With Metastatic Castration-resistant Prostate Cancer and Homologous Recombination Gene Deficiency (TRITON3)

Major Goals: The major goal of this study is to assess the efficacy of rucaparib versus physician's choice of treatment based on radiographic progression free survival (rPFS) in mCRPC patients with HRD who progressed on prior AR-directed therapy and have not yet received chemotherapy in the castration-resistant setting.
Status of Support: Active
Project Number: CO-338-063
Name of PD/PI: Celestia Higano (2018-2021) Heather Cheng (2021 – Present)
Source of Support: Clovis Oncology
Primary Place of Performance: Fred Hutch Cancer Center – Seattle, WA
Project/Proposal Start and End Date: 8/21/2018 – 4/30/2023
Total Award Amount:

Title: AMPLITUDE A Study of Niraparib in Combination With Abiraterone Acetate and Prednisone Versus Abiraterone Acetate and Prednisone for the Treatment of Participants With Deleterious Germline or Somatic Homologous Recombination Repair (HRR) Gene-Mutated Metastatic Castration-Sensitive Prostate Cancer
Major Goals: The major goal of this study is to assess the primary endpoint, rPFS, and defined as the time from the date of the randomization to the date of radiographic progression, or death.
Status of Support: Active
Project Number: 67652000PCR3002
Name of PD/PI: Heather Cheng
Source of Support: Janssen Research & Development, LLC
Primary Place of Performance: Fred Hutch Cancer Center – Seattle, WA
Project/Proposal Start and End Date: 8/16/2021 – 1/31/2026
Total Award Amount:

Title: A Phase 1, open label study evaluating the safety, pharmacokinetics and clinical effects of intravenously administered PT-112 injecting in patients with advanced solid tumors and subsequent expansion cohorts
Major Goals: Define the recommended dose level for PT-112, administered on Days 1 and 15 of each 28-day cycle, for pivotal studies based on the risk/benefit ratio of 360 mg/m2 (Arm 1) and 250 mg/m2 (Arm 2) dose levels.
Status of Support: Active
Project Number: PT-112-101
Name of PD/PI: Heather Cheng
Source of Support: Phosplatin Therapeutics LLC
Supporting Agency: Phosplatin Therapeutics LLC
Primary Place of Performance: Fred Hutch Cancer Center – Seattle, WA
Project/Proposal Start and End Date: 9/28/21 – 7/31/2026
Total Award Amount:

Title: Prostate Cancer Outcomes: An International Registry to Improve Outcomes in Men with Advanced Prostate Cancer (IRONMAN)
Major Goals: The major goal of this study is to create an international, population-based, prospective registry of at least 5,000 men with advanced prostate cancer.
Status of Support: Active
Project Number: C16-170
Name of PD/PI: Heather Cheng
Source of Support: Movember (via PCCTC, LLC)
Primary Place of Performance: Fred Hutch Cancer Center – Seattle, WA
Project/Proposal Start and End Date: 08/18/17 to 01/31/2029
Total Award Amount:

Title: IRONMAN: An International Registry and/or the PMC Sub-Study for Men with Advanced Prostate Cancer
Major Goals: The primary objective of this substudy is to describe the response and DOR to olaparib

among subjects with mCRPC whose disease has progressed following prior treatment with an NHA. Subjects with a mutation in one of the nine HRR genes (BARD1, BRIP1, CHEK1, FANCL, PALB2, RAD51B, RAD51C, RAD51D, and RAD54L) that were evaluated in five or fewer subjects within cohort B of the PROfound study will be included in the study.
Status of Support: Active
Project Number: C16-170a
Name of PD/PI: Heather Cheng
Source of Support: AstraZeneca Pharmaceuticals, LP (via PCCTC, LLC)
Primary Place of Performance: Fred Hutch Cancer Center – Seattle, WA
Project/Proposal Start and End Date: 08/18/17 to 01/31/2029
Total Award Amount:

Title: Long-read DNA-sequencing and targeted RNA-Seq to identify previously undetectable classes of mutations in families with lethal prostate cancer.
Major Goals: We intend our approach to improve genetic testing for inherited predisposition to prostate cancer, particularly in families with a severe history of the disease but no genetic diagnosis. We will Inform all patients with positive test results and integrate new genetic information into their care following NCCN guidelines for mutation carriers and offer genetic testing to their family members. As such, our proposal specifically addresses the overarching challenge of reducing lethal prostate cancer in high risk populations.
Status of Support: Active
Project Number: W81XWH-21-1-0343
Name of PD/PI: Tomas D. Walsh
Source of Support: US Department of Defense (DOD)
Primary Place of Performance: University of Washington Medical Center – Seattle, WA
Project/Proposal Start and End Date: 06/01/2021 – 05/31/2024
Total Award Amount:

PENDING RESEARCH SUPPORT

Title: Pacific Northwest (PNW) Prostate Cancer Sponsored Program of Research Excellence (SPORE) Project 1: Molecular Predictors of Prostate Cancer Progression and Mortality
Major Goals: The major goals of the study are to define the independent and combined effect of multi-ancestry PRS (PRS_m) and gDRG with clinical characteristics of prostate cancer aggressiveness and prognosis across diverse populations. To develop clinical-grade paired tumor-germline molecular profiling assays to prospectively interrogate multi-ancestry PRS and gDRG. And to conduct a tailored prostate cancer screening clinical trial for at-risk men with gDRG and determine patterns of enrollment and adherence.
Status of Support: Pending
Project Number: PAR-20-305
Name of PD/PI: Peter Nelson
Source of Support: NIH/NCI
Primary Place of Performance: Fred Hutch Cancer Center – Seattle, WA
Project/Proposal Start and End Date: 09/01/23 - 08/31/28
Total Award Amount:

Title: NCI R50 Research Specialist (Clinician Scientist)
Major Goals: The project goals are to continue contribution to NCI and NCTN supported clinical/translational research, mentoring clinical scientists, and developing novel approaches to clinical research and to education and outreach for patients with the goal of accruing a more representative cohort of patients to the next generation of targeted and patient-partnered clinical trials.
Status of Support: Pending
Project Number: PAR-20-306
Name of PD/PI: Heather Cheng
Source of Support: NIH/NCI

Primary Place of Performance: Fred Hutch Cancer Center – Seattle, WA
Project/Proposal Start and End Date: 07/01/2023-6/30/2028
Total Award Amount:

COMPLETED RESEARCH SUPPORT

1998	New Jersey Cancer Commission Research Fellowship
1998-2000	NIH Medical Scientist Training Program Fellowship
2000-2004	Paul Allen Research Fellowship
2010-2013	NIH T32 Training in Cancer Biology and Transplantation Fellowship

Title: SWOG 1216: A phase III randomized trial comparing androgen deprivation therapy + TAK-700 with androgen deprivation therapy + bicalutamide in patients with newly diagnosed metastatic hormone sensitive prostate cancer
Supporting Agency: NIH/NCI (U10 CA180828)
Performance Period: 05/20/14 – 02/28/18
Level of Funding:
Project Goals: Compare overall survival in newly diagnosed metastatic prostate cancer patients randomly assigned to androgen deprivation therapy (ADT) (LHRHa or orchiectomy) + TAK-700 versus ADT (LHRHa or orchiectomy) + bicalutamide.

Title: Genitourinary Cancer Clinical Research Database Support
Supporting Agency: Institute for Prostate Cancer Research (IPCR)
Performance Period: 09/01/14 – 12/31/19
Level of Funding:
Project Goals: The GU Cancer Clinical Research Database (GUCCRD) is designed to inventory, display, aggregate, and integrate comprehensive clinical information derived from patients with prostate cancer (and potentially other GU malignancies).

Title: Cancer Center Support Grant: New Investigator Award
Supporting Agency: NIH/NCI (P30 CA015704)
Performance Period: 12/15/14 – 12/31/19
Level of Funding:
Project Goals: The major goal of this project is to recruit new investigators who will further the strategic objectives of the University of Washington/Fred Hutchinson Cancer Consortium. Specifically, this project will develop infrastructure to study the underlying genetic causes of early onset prostate cancer and familial prostate cancer.

Title: Defining the role of cancer risk genes in early-onset, lethal prostate cancer
Supporting Agency: NIH/NCI (P50 CA097186)
Performance Period: 01/01/15 – 12/31/15
Level of Funding:
Project Goals: The major goal of this project is to examine the role of germline cancer risk genes in early-onset, lethal prostate cancer and parlay the resulting data into future research projects.

Title: Identifying germline cancer risk genes in advanced prostate cancer
Supporting Agency: NIH/NCI (P50 CA097186)
Performance Period: 01/01/15 – 08/31/16
Level of Funding:
Project Goals: The major goal of this project is to identify the underlying genetic cause in some hereditary prostate cancer families--especially those with early-onset, aggressive prostate cancer--by examining tumor suppressor genes known to be involved in other familial cancer syndromes.

Title: A precision clinical trial targeting DNA repair defects
Supporting Agency: Institute for Prostate Cancer Research (IPCR)

Performance Period: 07/01/15 – 12/31/19
Level of Funding:
Project Goals: The major goal of this project is to determine if men with tumors that harbor DNA repair defects will exhibit the hypothesized enhanced sensitivity to platinum-based chemotherapy.

Title: 2016 Challenge Award: Exploiting DNA repair vulnerabilities as a precision oncology target in metastatic prostate cancer
Supporting Agency: Movember Foundation & Prostate Cancer Foundation
Performance Period: 07/31/15 – 07/31/18
Level of Funding:
Project Goals: The major goal of this project is to test the hypothesis that aberrations in key genes that repair DNA strand breaks by homologous repair are predictive of meaningful clinical responses to FDA-approved genotoxic therapeutics.

Title: 2015 PCF Young Investigator Award: Identifying high-penetrance prostate cancer risk genes: leveraging families for next generation discovery and prevention
Supporting Agency: Prostate Cancer Foundation
Performance Period: 10/01/15 – 09/30/18
Level of Funding:
Project Goals: The major goals of this project are to collect families affected by prostate cancer and discover new prostate cancer risk genes, to collect men with prostate cancer who are found via tumor testing to carry high-penetrance germline cancer risk mutations, and to provide both groups of men and their family members with access to better educational materials, genetic counseling resources, and research opportunities.

Title: PCa-001: Phase I, open-label trial to evaluate the safety and immugenicity of INO-5150 alone or in combination with INO-9012 in men with biochemically relapsed (PSA) prostate cancer
Supporting Agency: Inovio Pharmaceuticals
Performance Period: 11/12/15 – 11/11/18
Level of Funding:
Project Goals: The major goal of this study is to test the study drug INO-5150 (plasmid DNA vaccine) for prostate specific proteins alone or in combination with INO-9012 (plasmid DNA vaccine for human interleukin 12) to see how safe they are and if they cause any side effects or generate an immune response against prostate cancer cells when given by intramuscular injection followed by electroporation.

Title: Pharmacogenetic dissection of protein synthesis control across the spectrum of PI3K pathway mutations in prostate cancer
Supporting Agency: Movember Foundation & Prostate Cancer Foundation (2016CHAL1523)
Performance Period: 10/01/16 – 09/30/18
Level of Funding:
Project Goals: The major goal of this project is to delineate the biology of various PI3K pathway mutations that occur in CRPC and develop strategies to effectively target tumors harboring these mutations.

Title: CRISPR-excision and long-read sequencing of BRCA1, BRCA2, PALB2 and ATM to identify previously undetectable classes of mutations in families severely affected with advanced prostate cancer (PIs Tom Walsh, Heather Cheng)
Level (%) of effort: 10%
Funding Agency: Brotman Baty Institute
Performance period: 02/01/2020 to 01/31/2021

Total level of Funding:
Goals of the project: The goal is to identify complex structural mutations in advanced prostate cancer families that have been missed by current sequencing approaches.
Title: Telehealth to Reduce Prostate Cancer Burden in Rural Underserved Communities
Effort: 0.30 calendar
Supporting Agency: Fred Hutchinson Cancer Research Center CCSG (NIH)

Contracting/Grants Officer: Heidi Tham
Performance Period: 07/01/18 to 12/31/21
Level of Funding:
Project Goals: The major goal of this study is to provide prostate cancer patients in rural areas with access to treatment options and resources they may not otherwise receive from a general practitioner.
Specific Aims: 1) Evaluate the telehealth program through patient-reported outcomes, 2) assess some clinician-directed and health system-responsiveness outcomes, and 3) specifically assess the outcomes in the prostate cancer Genetics Clinic, with an eye toward developing a model on which to base other niche clinics in genitourinary oncology.

Title: A phase 1b study of enzalutamide plus CC-115 in men with castration-resistant prostate cancer
Effort: 0.60 calendar
Supporting Agency: PCCTC, LLC (Celgene)
Performance Period: 10/01/17 to 12/31/21
Level of Funding:
Project Goals: The major goal of this study is to determine the safety, pharmacokinetics, and the Maximum Tolerated Dose and/or Recommended Phase 2 Dose of the combination of CC-115 plus enzalutamide.

Title: A ph I/II trial of concurrent chemohormonal therapy using enzalutamide (MDV-3100) and cabazitaxel in patients with metastatic castration resistant prostate cancer
Effort: 0.60 calendar
Supporting Agency: PCCTC, LLC (Medivation and Sanofi)
Performance Period: 07/14/16 to 11/30/21
Level of Funding:
Project Goals: The major goal of this project is to test the safety and efficacy of combination treatment with enzalutamide (MDV3100) and cabazitaxel chemotherapy of prostate cancer.
Specific Aims: To determine safe dosing level. To collect correlative biospecimens to understand the biological effects of the treatment and to evaluate for potential prognostic biomarkers.

Title: The Galahad Study: A phase 2 efficacy and safety study of niraparib in men with metastatic castration-resistant prostate cancer and DNA-repair anomalies
Effort: 0.60 calendar
Supporting Agency: Janssen Research & Development, LLC
Performance Period: 12/28/16 to 12/27/21
Level of Funding:
Project Goals: The major goal of this project is to assess the efficacy of niraparib in men with mCRPC and DNA-repair anomalies who have measurable disease by looking at the objective response rate.
Specific Aims: To assess the efficacy of niraparib in subjects with mCRPC and DNA-repair anomalies.

Title: A ph I/II trial of concurrent chemohormonal therapy using enzalutamide (MDV-3100) and cabazitaxel in patients with metastatic castration resistant prostate cancer.
Major Goals: To determine safe dosing level. To collect correlative biospecimens to understand the biological effects of the treatment and to evaluate for potential prognostic biomarkers. The major goal of this project is to test the safety and efficacy of combination treatment with enzalutamide (MDV3100) and cabazitaxel chemotherapy of prostate cancer.
Status of Support: Active
Project Number: MDV3100
Name of PD/PI: Heather Cheng
Source of Support: PCCTC, LLC (Medivation and Sanofi)
Primary Place of Performance: Fred Hutch Cancer Center – Seattle, WA
Project/Proposal Start and End Date: 07/14/16 to 11/30/22
Total Award Amount:

Title: PROSTATE CANCER CLINICAL TRIALS CONSORTIUM, W81XWH-17-2-0043 (Cheng)
Major Goals: The Department of Defense provides funding for infrastructure to support participation as

a clinical site in the Prostate Cancer Clinical Trials Consortium.
Status of Support: Active
Project Number: W81XWH-17-2-0043
Name of PD/PI: Heather Cheng
Source of Support: US Department of Defense (DOD)
Primary Place of Performance: Fred Hutch Cancer Center – Seattle, WA
Project/Proposal Start and End Date: 09/30/2017 to 09/29/2022
Total Award Amount:

Title: Technology-Enhanced Acceleration of Germline Evaluation for Therapy - The TARGET Study
Major Goals: The proposed study will 1) evaluate understanding of providers around genetic testing in prostate cancer patients and uncover barriers to identifying patients who meet the NCCN guidelines for genetic testing. 2) develop a mobile app to assist providers in educating patients and identifying candidates for genetic testing. 3) devise a randomized clinical trial comparing mobile-assisted app to traditional, in-person genetic counseling for men with metastatic prostate cancer in different practice settings.
Status of Support: Active
Project Number: 080-27000-U23201
Name of PD/PI: Heather Cheng
Source of Support: Prostate Cancer Foundation
Primary Place of Performance: Fred Hutch Cancer Center – Seattle, WA
Project/Proposal Start and End Date: 08/06/20 – 12/31/2022
Total Award Amount:

Title: Clinical qualification of DNA repair defects as biomarkers in metastatic prostate cancer using integrated genomics and tissue-based functional assays.
Major Goals: We aim to evaluate tissue-based tests of HR proficiency to stratify patients to receive DNA repair targeting agents. In a two-step approach, we will optimize the test and study the correlation with genomic data in a cohort of mCRPC biopsies, to then implement the assay into a clinical trial to stratify patients for receiving treatment with carboplatin, a DNA damaging chemotherapy.
Status of Support: Active
Project Number: W81XWH-15-1-0430
Name of PD/PI: Colin Pritchard
Source of Support: US Department of Defense (DOD)
Primary Place of Performance: Fred Hutch Cancer Center – Seattle, WA
Project/Proposal Start and End Date: 09/30/18 to 09/29/22
Total Award Amount:

Title: A phase 1b study of enzalutamide plus CC-115 in men with castration-resistant prostate cancer.
Major Goals: The major goal of this study is to determine the safety, pharmacokinetics, and the Maximum Tolerated Dose and/or Recommended Phase 2 Dose of the combination of CC-115 plus enzalutamide.
Status of Support: Active
Project Number: CC-115
Name of PD/PI: Heather Cheng
Source of Support: PCCTC, LLC (Celgene)
Primary Place of Performance: Fred Hutch Cancer Center – Seattle, WA
Project/Proposal Start and End Date: 10/01/17 to 12/31/22
Total Award Amount:

17. Bibliography:

Scopus Index (1/5/2023)
h-index: 26
Cumulative citations:

Google Scholar, All (1/5/2023)
h-index: 30
Cumulative citations: 10,019

a) Publications in Refereed Journals

1. Pöpperl H, Rikhof H, **Cheng H.**, Haffter P, Kimmel CB, Moens CB. lazarus is a novel pbx gene that globally mediates hox gene function in zebrafish. Molecular Cell. 2000 Aug; 6(2): 255-267. [**original work**]

2. Lauring, A.S., **Cheng, H.H.**, Eiden, M.V., and Overbaugh, J. Genetic and biochemical analyses of receptor and cofactor determinants for T-cell-tropic feline leukemia virus infection. Journal of Virology. 2002 Aug; 76(16): 8069-8078. [**original work**]

3. **Cheng, H.H**., Anderson, M.M., Hankenson, F.C., Johnston, L., Kotwaliwale, C.V., Overbaugh, J. Envelope determinants for dual-receptor specificity in feline leukemia virus subgroup A and T variants. Journal of Virology. 2006 Feb; 80(4): 1619-1628. [**original work**]

4. **Cheng, H.H.**, Anderson, M.M., Overbaugh, J. Feline Leukemia Virus T entry is dependent on both expression levels and specific interactions between cofactor and receptor. Virology. 2007 Mar; 359(1): 170-178. [**original work**]

5. Pritchard, C.C., **Cheng, H.H.**, Tewari, M. MicroRNA Profiling: approaches and considerations. Nature Reviews Genetics. 2012 Apr 18; 13(5): 358-69. **[review]**

6. **Cheng, H.H.,** Lin, D., Yu, E.Y. Advanced Clinical States in Prostate Cancer. Urologic Clinics of North America. 2012 Nov;39 (4):561-71. **[review]**

7. **Cheng, H.H.,** Yi, H.S., Kim, Y., Kroh, E., Goodman, M., Chien, J., Tait, J.F., Tewari, M., Pritchard, C.C. Plasma processing conditions substantially influence circulating microRNA biomarker levels. PLoS ONE 2013 Jun 7;8(6). [**original work**] ***One of the top 1% of most highly cited articles in PLoS ONE.***

8. **Cheng, H.H.,** Mitchell, P.S., Kroh, E., Dowell, A.E., Chéry, L., Siddique J., Nelson, P.S., Vessella, R., Knudsen, B.S., Chinnaiyan, A.M., Pienta, K.J., Morrissey, C., Tewari, M. Circulating microRNA Profiling Identifies a Subset of Metastatic Prostate Cancer Patients with Evidence of Cancer-Associated Hypoxia, PLoS ONE, 2013 Jul 30;8(7). [**original work**]

9. Lee, F., Harris, W.P., **Cheng, H.H.**, Shenoi, J., Zhao, S., Wang, J., Champion, T., Izard, J., Gore, J.L., Porter, M.P., Yu, E.Y., Wright, J.L. Pathologic Response Rates of Gemcitabine/Cisplatin VS. Methotrexate/Vinblastine/Adriamycin/Cisplatin Neoadjuvant Chemotherapy for Muscle Invasive Urothelial Bladder Cancer. Advances in Urology, 2013; 2013:317190. [**original work**]

10. Mossanen, M., Lee, F., **Cheng, H.H.**, Harris, W., Shenoi, J., Zhao, S., Wang, J., Champion, T., Izard, J., Gore, J.L., Porter, M.P., Yu, E.Y., Wright, J.L. Non-Response to Neoadjuvant Chemotherapy for Muscle Invasive Urothelial Cell Carcinoma of the Bladder. Clinical Genitourinary Cancer, 2013 Nov 12. [**original work**]

11. James, A.C., Lee, F.C., Izard, J.P., Harris, W.P., **Cheng, H.H.,** Zhao, S., Gore, J.L., Lin, D.W., Porter, M.P., Yu, E.Y., Wright, J.L. Role of maximal endoscopic resection prior to cystectomy for invasive urothelial bladder cancer. Clinical Genitourinary Cancer, 2014 Jan 23. [**original work**]

12. Montgomery, R.B., **Cheng, H.H.,** Drechsler, J., Mostaghel, E.A. Glucocorticoids and prostate cancer treatment: Friend or foe? Asian Journal of Andrology, 2014 Mar 7. **[review]**

13. **Cheng, H.H.** and Higano. C.S. Targeting the AR signaling axis: how low to go? Oncology, 2014 Aug 15. **[editorial]**

14. Ramos, J.D., **Cheng, H.H.,** Yu, E.Y. Long-term survival in bone-predominant metastatic urothelial carcinoma. Clinical Genitourinary Cancer, 2014 Jul 23. **[case report]**

15. Chevillet, J.R., Kang, Q., Ruf, I.K., Briggs, H.A., Vojtech, L.N., Hughes, S.M., **Cheng, H.H.**, Arroyo, J.D., Knouf, E.C., Gallichotte, E.N., Pogosova-Agadjanyan, E.L., Vessella, R.L., Stirewalt, D.L., Hladik, F., Yu, E.Y., Higano, C.S., Tewari, M. Quantitative and stoichiometric analysis of the microRNA content of exosomes, PNAS, 2014 Oct 14. **[original work]**

16. **Cheng, H.H.,** Gulati, R., Azad, A.A., Nadal, R., Twardowski, P., Vaishampayan, U.N., Agarwal, N., Heath, E.I., Pal, S.K., Rehman, H., Leiter, A., Batten, J.A., Montgomery, R.B., Galsky, M.D., Antonarakis, E.S., Chi, K.N., Yu, E.Y. Activity of enzalutamide in men with metastatic castration resistant prostate cancer depends on prior treatment with abiraterone and/or chemotherapy. Prostate Cancer and Prostatic Diseases, 2015 Jan 20. **[original work]**

17. Yu, E.Y., Li, H., Higano, C.S., Agarwal, N., Pal, S.K., Alva, A., Heath, E.I., Lam, E.T., Gupta, S., Lilly, M.B., Inoue, Y., Chi, K.N., Vogelzang, N.J., Quinn, D.I., Li, H., **Cheng, H.H.,** Plymate, S.R., Hussain, M.H., Thompson, I.M. SWOG S0925: A randomized phase 2 study of androgen deprivation combined with cixutumumab (IMC-A12) versus androgen deprivation alone for patients with new metastatic castration-sensitive prostate cancer. Journal of Clinical Oncology, 2015 Apr 6. **[original work]**

18. **Cheng, H.H.**, Soleau, C., Yu, E.Y. Improved disease markers suggest dual response in a patient with metastatic castration resistant prostate cancer and chronic lymphocytic leukemia following active cellular immunotherapy. Journal of Hematology and Oncology, Journal of Hematology and Oncology, 2015 May 14**. [case report]**

19. **Robinson, D, Van Allen, E.M., Wu, Y, Schultz, N., Lonigro, R.J., Mosquera, J., Montgomery, R., Taplin, M.E., Pritchard, C.C., Attard, G., Beltran, H., Abida, W.M., Bradley, R.K., Vinson, J., Cao, X., Vats, P., Kunju, L.P., Hussain, M., Feng, F.Y., Tomlins, S.A., Cooney, K.A., Smith, D.C., Brennan, C., Siddiqui, J., Mehra, R., Scher, H.I., Chen, Y., Rathkopf, D.E., Morris, M.J., Solomon, S.B.,Durack, J.C., Reuter, V.E., Gopalan, A., Gao, J., Loda, M., Lis, R.T., Bowden, M., Balk, S.P., Gaviola, G., Sougnez, C., Gupta, M., Yu, E.Y., Mostaghel, E.A., **Cheng, H.H.,** Chew, F.S., True, L.D., Plymate, S.R., Dvinge, H., Ferraldeschi, R., Flohr, P., Miranda, S., Zafeiriou, Z., Tunariu, N., Mateo, J., Demichelis, F., Elemento, O., Robinson, B.D., Sboner, A., Schiffman, M.A., Nanus, D.M., Tagawa, S.T., Sigaras, A., Eng, K.W., Heath, E., Pienta, K.J., Kantoff, P., de Bono, J.S., Rubin, M.A., Nelson, P.S., Garraway, L.A., Sawyers, C.L., Chinnaiyan, A.M. Integrative clinical sequencing analysis of metastatic castration resistant prostate cancer reveals a high frequency of clinical actionability. Cell, 2015 May 21. **[original work]**

20. ****Cheng, H.H.,** Pritchard, C.C., Boyd, T., Nelson, P.S., Montgomery, R.B. Biallelic inactivation of *BRCA2* in metastatic castration resistant prostate cancer and platinum sensitivity*;* European Urology, 2016, *Epub.* **[original work]** ***Selected as one of the Highlights of June 2016 issue.***

21. **Cheng, H.H.*,** Klemfuss, N., Montgomery, B., Higano, C.S., Schweizer, M.T., Mostaghel, E.H., McFerrin, L.G., Yu, E.Y., Nelson, P.S., Pritchard, C.C. Pilot study of clinical targeted next generation sequencing for prostate cancer: consequences for treatment and genetic counseling. The Prostate*,* 2016 Jun 21. [**original work]** *(*HHC corresponding author*)

22. Schweizer, M.T., Gulati, R., Mostaghel, E.M., Nelson, P.S., Montgomery, B., Yu, E.Y., **Cheng, H.H.** Docetaxel-Related Toxicity in Metastatic Hormone-Sensitive Versus Castration-Resistant Prostate Cancer; Medical Oncology, 2016 Jul. **[original work]**

23. **Pritchard, C.C., Mateo, J., Walsh, M.F., De Sarkar, N., Abida, W., Beltran, H., Garofalo, A., Gulati, R., Carreira, S., Eeles, R., Elemento, O., Rubin, M.A., Robinson, D., Lonigro, R., Hussain, M., Chinnaiyan, A.M., Vinson, J., Filipenko, J., Garraway, L.A., Taplin, M-E, AlDubayan, S., Celine Han, G., Beightol, M., Morrissey, C., Ngheim, B., **Cheng, H.H**., Montgomery, B., Walsh, T., Casadei, S., Berger, M.,

Zhang, L., Zehir, A., Vijai, J., Scher, H.I., Sawyers, C., Schultz, N., Kantoff, P., Solit, D., Robson, M., Van Allen, E.M., Offitt, K., De Bono, J.S., Nelson, P.S. Inherited DNA Repair Gene Mutations in Men with Metastatic Prostate Cancer; New England Journal of Medicine, 2016 Jul 6. **[original work]**

24. Schweizer, M.T.*, **Cheng, H.H**.*, Tretiakova, M.S., Vakar-Lopez, F., Klemfuss, N., Mostaghel, E.A., Morrissey, C., Nelson, P.S., Yu, E.Y., Montgomery, R.B., True, L.D., Pritchard, C.C., Mismatch Repair Deficiency is Common in Ductal Prostatic Adenocarcinoma. Oncotarget, 2016, Oct. **[original work]** *(*co-first authorship*)

25. Gulati, R., **Cheng, H.H.**, Lange, P.H., Nelson, P.S., Etzioni, R. Screening men at increased risk for prostate cancer diagnosis: Model estimates of benefits and harms. Cancer Epidemiology Biomarkers and Prevention, 2016, Oct. **[original work]**

26. **Cheng, H.H.*,** Pritchard, C.C., Montgomery, B., Lin, D.W., Nelson, P.S. Prostate Cancer Screening in a New Era of Genetics. Clinical Genitourinary Cancer, 2017, May 31. **[editorial]** *(*HHC corresponding author*)

27. Miyahira, A.K., **Cheng, H.H.,** Abida, W., Ellis, L., Harshman, L., Spratt, D., Simons, J.W., Pienta, K.J., and Soule, H.R. Beyond the Androgen Receptor II: New Approaches to Understanding and Treating Metastatic Prostate Cancer; Report from the 2017 Coffey-Holden Prostate Cancer Academy Meeting. The Prostate, 2017, Sept 18. [**review**]

28. Ly, A., **Cheng, H.H.**, Alwan, L. Hepatitis C infection and chemotherapy toxicity. Journal of Oncology Pharmacy Practice, 2018, Jan 1. [**case series**]

29. **Cheng, H.H.,** Plets, M., Li, H., Higano, C.S., Agarwal, N., Vogelzang, N.J., Hussain, M., Thompson, I.M., Tewari, M., Yu, E.Y. Circulating microRNAs and treatment response in the Phase II SWOG S0925 study for patients with new metastatic hormone-sensitive prostate cancer. The Prostate, 2018, Feb. **[original work]**

30. ****Cheng, H.H.**, Salipante, S., Nelson, P.S., Montgomery, B., Pritchard, C.C. Polyclonal *BRCA2* reversion mutations detected in circulating tumor DNA after platinum chemotherapy in a patient with metastatic prostate cancer. JCO Precision Oncology, 2018 Feb 14. **[case report]**

31. Mateo, J.*, **Cheng, H.H.*,** Beltran, H.*, Dolling, D., Xu, W., Pritchard, C.C., Mossop, H., Rescigno, P., Perez-Lopez, R., Kolinsky, M., Balasapoulou, A., Carreira, S., Thorne, H., Montgomery, B., Sandhu, S., Rubin, M.A., Nelson, P., de Bono, J.S. Clinical Outcomes of Prostate Cancer Patients with Germline DNA Repair Mutations: Follow-up from an International Study, European Urology, 2018 Jan 29. *(*co-first authorship)* **[original work]**

32. **Cheng, H.H.,** The Resounding Impact of DNA Repair Deficiency in Prostate Cancer. Urologic Oncology, 2018 Mar 16 **[editorial]**

33. Schweizer, M.T., Haugk, K., McKiernan, J.S., Gulati, R., **Cheng, H.H.,** Maes, J.L., Dumpit, R.F., Nelson, P.S., Montgomery, B., McCune, J.S., Plymate, S.R., Yu, E.Y. A Phase I Study of Niclosamide in Combination with Enzalutamide in Men with Castration-Resistant Prostate Cancer. PLOS ONE, 2018 June 1. **[original work]**

34. **Cheng, H.H.*,** Powers, J., Schaffer, K., Sartor, O., Practical Methods for Integrating Genetic Testing Into Clinical Practice for Advanced Prostate Cancer. Am Soc Clin Oncol Educ Book, 2018 May 23. *(*HHC corresponding author*) [**review**]

35. Lim, D.M., Gulati, R., Aleshin-Guendel, S., Gawne, A., Wingate, J.T., **Cheng, H.H**., Etzioni, R., Yu, E.Y., Undetectable Prostate-Specific Antigen After Short-Course Androgen Deprivation Therapy for Biochemically-Recurrent Prostate Cancer Patients Correlates with Time to Metastasis and Prostate Cancer-Specific Survival. The Prostate, 2018 Jul 10. **[original work]**

36. Carlo, M.I., Giri, V.N., Paller, C.S., Abida, W., Alumkal, J.J., Beer, T.M., Beltran, H., George, D.J., Heath, E.I., Higano, C.S., McKay, R.R., Morgans, A.K., Patnaik, A., Ryan, C.J., Schaeffer, E.M., Stadler, W.M., Kauff, N.D., Vinson, J., Antonarakis, E.S., **Cheng, H.H.*** Evolving Intersection Between Inherited Cancer Genetics and Therapeutic Clinical Trials in Prostate Cancer: A White Paper from the Germline Genetics Working Group of the Prostate Cancer Clinical Trials Consortium. JCO Precision Oncology, 2018 Aug 16. *(*HHC corresponding author*) **[original work]**

37. Hahn, A.W. Stenehjem, D.D., Alex, A.B., Esther, J. Gill, D.M., **Cheng, H.H.,** Kessler, E.R., Chittoria, N., Twardowski, P., Vaishampayan, U., Agarwal, N. Time from definitive therapy to onset of metastatic disease predicts outcomes in men with metastatic hormone sensitive prostate cancer. Urologic Oncology, 2019 Feb 13. **[original work]**

38. Schweizer, M.T., Gulati, R., Beightol, M., Konnick, E.Q., **Cheng, H.H**., de Sarkar, N., Yu, E.Y., Montgomery, R.B., Nelson, P.S., Pritchard, C.C. Clinical determinants for Successful Circulating Tumor DNA Analysis in Prostate Cancer. The Prostate, 2019 March 13. **[original work]**

39. Marshall, C.H., Sokolova, A.O., McNatty, A.L., **Cheng, H.H.,** Eisenberger, M.A., Bryce, A.H., Schweizer, M.T., Antonarakis, E.S. Differential response to olaparib therapy in men with metastatic castration-resistant prostate cancer harboring *BRCA1* or *BRCA2* versus *ATM* mutations. European Urology, 2019 Feb 21. **[original work]**

40. Schweizer, M.T., Antonarakis, E.S., Bismar, T.A., Guedes, L.B., **Cheng, H.H.,** Tretiakova, M.S., Vakar-Lopez, F., Klemfuss, N., Konnick, E.Q., Mostaghel, E.A., Hsieh, A.C., Nelson, P.S., Yu, E.Y., Montgomery, R.B., True, L.D., Epstein, J.I., Lotan, T.L., Pritchard, C.C. Genomic characterization of prostatic ductal adenocarcinoma identifies a high prevalence of DNA repair gene mutations. JCO Precis Oncol, 2019 Apr 18. **[original work]**

41. **Cheng, H.H.*,** Sokolova, A.O., Schaeffer, E.M., Small, E., Higano, C.S. Germline and Somatic Mutations in Prostate Cancer. Journal of the National Comprehensive Cancer Network, 2019 May 1;17(5):515-521. *(*HHC corresponding author*) **[review]**

42. Paller, C.J., Antonarakis, E.S.**,** Beer, T.M., Borno, H.T., Carlo, M.I., George, D.J., Graff, J.N., Gupta, S., Heath, E.I., Higano, C.S., McKay, R.R., Morgans, A.K., Patnaik, A., Petrylak, D.P., Rettig, M.B., Ryan, C.J., Taplin, M.E., Whang, Y.E., Vinson, J., **Cheng, H.H.***, Giri, V.N.* Germline Genetic Testing in Advanced Prostate Cancer - Practices and Barriers: Survey Results from the Germline Genetics Working Group of the Prostate Cancer Clinical Trials Consortium. Clin Genitourin Cancer. 2019 Apr 18. *(*HHC co-corresponding author*) **[original work]**

43. Winters, B., De Sarkar, N., Arora, S., Bolouri, H., Jana, S., Vakar-Lopez, F., **Cheng, H.H.,** Schweizer, M.T., Yu, E.Y., Grivas, P., Lee, J.K., Montgomery, B., Schweizer, M., Hsieh, A., Yu, E., Lee, J.K., Kollath, L., Holt, S.K., McFerrin, L., Ha, G., Nelson, P.S., Montgomery, R.B., Wright, J.L., Lam, H. Hsieh, A.C. Genomic distinctions between metastatic lower and upper tract urothelial carcinoma revealed through rapid autopsy. *Journal Clinical Investigation Insight.* 2019 May 30. **[original work]**

44. Labrecque, M.P., Coleman, I.M., Brown L.G., True, L.D., Kollath, L., Lakely, B., Holly M. Nguyen., H.M., Yang,Y.C., Kaipainen, A.H., Coleman, R.T., Higano, C.S., Yu, E.Y**., Cheng, H.H.,** Mostaghel, E.A., Montgomery, B., Schweizer, M.T., Hsieh, A.C., Lin, D.W., Corey, E., Nelson, P.S., Morrissey, C. Molecular Profiling Stratifies Diverse Phenotypes of Treatment-refractory Metastatic Castration Resistant Prostate Cancer. *Journal of Clinical Investigation.* 2019 July 20. **[original work]**

45. Kwon D.H., Borno H.T., **Cheng H.H.,** Small E.J. Ethnic disparities among men with prostate cancer undergoing germline testing. *Urologic Oncology: Seminars and Original Investigations.* 2019 Oct 17. **[original work]**

46. **Cheng, H.H.** Germline Contributions to Metastatic Prostate Cancer. *Canadian Journal of Urology.* 2019 Oct; 26(5S2): 12-21 *(*HHC corresponding author*) **[review]**

47. Mohler, J.L., Higano, C.S., Schaeffer, E.M., **Cheng, H.H.,** Current Recommendations for Prostate Cancer Genetic Testing: NCCN Prostate Guideline. *Canadian Journal of Urology.* 2019 Oct; 26(5S2): 34-37. **[review]**

48. Narayan V, Harrison M, **Cheng H.H.,** Kenfield S, Aggarwal R, Kwon D, McKay R, Hauger R, Hart N, Conzen S, Borno H, Jim H, Dicker A, Dorff T, Moslehi J, Mucci L, Parsons JK, Saad F, Soule H, Morgans AK, Ryan CJ. Improving Research for Prostate Cancer Survivorship: A Consensus Statement from the SuRECaP (Survivorship Research in Prostate Cancer) Working Group. *Urologic Oncology: Seminars and Original Investigation.* 2020 Mar; 38(3):83-93 **[review]**

49. Sokolova, A.O., **Cheng, H.H.** Genetic Testing in Prostate Cancer. *Current Oncology Reports.* 2020 Jan 23; 22(1):5. *(*HHC corresponding author*) **[review]**

50. Shore, N.D., Morrow, M.P., McMullan, T., Kraynyak, K.A., Sylvester, A., Bhatt, K., Cheung, J., Boyer, J.D., Liu, L., Sacchetta, B., Rosencranz, S., Heath, E.I., Nordquist, L., **Cheng, H.H**., Tagawa, S.T., Appleman, L.J., Tutrone, R., Garcia, J., Whang, Y., Kelly, W.K., Bagarazzi, M., Skolnik, J.M. $CD8^+$ T Cells Impact Rising PSA in Biochemically Relapsed Cancer Patients Using Immunotherapy Targeting Tumor-Associated Antigens. *Mol Ther.* 2020 Mar 3. **[original work]**

51. Diamantopoulos, L.N., Winters, B., Grivas, P., Ngo, S.D., Zeng, J., Hsieh, A., Gore, J.L., Liao, J., Yu, E.Y., Schade, G., Schweizer, M.T., Lee, J., Dighe, M., Lin, D.W., **Cheng, H.H.,** Tretiakova, M., True, L., Russell, K., Vakar-Lopez, F., Montgomery, B., Wright, J.L. Bladder Cancer Multidisciplinary Clinic (BCMC) model: impact on treatment recommendations. *Bladder Cancer,* vol. 5, no. 4, pp. 289-298, 2019 **[original work]**

52. Wong, R.L., Duong, M.T., Tangen, C.M., Agarwal, N., **Cheng, H.H.,** Vogelzang, N.J., Hussain, M., Thompson, I.M., Quinn, D.I., Yu, E.Y., Final overall and progression-free survival outcomes from SWOG S0925, a randomized phase II study of androgen deprivation with cixutumumab versus androgen deprivation alone in patients with new metastatic hormone-sensitive prostate cancer. *Prostate Cancer Prostatic Dis.* 2020 Sep; 23(3): 486-493. **[original work]**

53. Chae, Y.K., Hong, F., Vaklavas, C., **Cheng, H.H.,** Hammerman, P., Mitchell, E., Zwiebel, J., Ivy, P., Gray, R., Li, S., McShane, L., Rubinstein, L., Patton, D., Williams, M., Hamilton, S., Mansfield, A., Conley. B., Arteaga, C., Harris, L.N., O'Dwyer, P., Chen, A., Flaherty, K. A Phase II Study of AZD4547 in Patients with Tumors harboring Aberrations in the FGFR Pathway: Results from the NCI-MATCH Trial (EAY131) Sub-protocol W. *Journal of Clinical Oncology,* 2020 May 28. **[original work]**

54. Sokolova, A.O., Shirts, B.H., Konnick, E.Q., Tykodi, S., Goulart, B.H.L., Montgomery, B., Pritchard, C.C., Yu, E.Y., **Cheng, H.H.** Complexities of Next Generation Sequencing for Solid Tumors: Case Studies in Interference from Clonal Hematopoiesis and Germline Variant Reclassification (*JNCCN,* 2020 September*:*18(9) *(*HHC corresponding author*) **[original work]**

55. Graham, L.S., Montgomery, B., **Cheng, H.H.,** Yu, E.Y., Nelson, P.S., Pritchard, C.C., Erickson, S., Alva, A., Schweizer, M.T. Mismatch Repair Deficiency in Metastatic Prostate Cancer (PC): Response to PD-1 Blockade and Standard Therapies. *PLOS ONE.* 2020 May 26; 15(5) **[original work]**

56. Sokolova, A.O., Yu, E.Y., **Cheng, H.H**., Honing in on PARPi response in Prostate Cancer: from HR pathway- to gene-by-gene granularity. *Clin Cancer Research.* 2020 June 1; 26(110):2439-2440 *(*HHC corresponding author*) **[commentary]**

57. Giri, V.N., Knudsen, K.E., Kelly, W.K., **Cheng, H.H.**, Cooney, K.A., Cookson, M., Dahut, W., Weissman, S., Soule, H., Petrylak, D., Dicker, A., Aldubayan, S., Toland, A., Pritchard, C.C., Pettaway, C., Daly, M.B., Mohler, J., Parsons, J.K., Carroll, P., Pilarski, R., Blanco, A., Woodson, A., Rahm, A.,

Taplin, M.E., Polascik, T., Helfand, B., Hyatt, C., Morgans, A.K., Feng, F., Mullane, M., Powers, J., Concepcion, R., Lin, D.W., Wender, R., Mark, J.R., Costello, A., Burnett, A., Sartor, A.O., Isaacs, W., Xu. J., Weitzel, J., Andriole, A., Beltran, H., Briganti, A., Byrne, L., Calvaresi, A., Chandrasekar, T., Chen, D., Den, R., Dobi, A., Crawford, D., Eastham, J., Eggener, S., Freedman, M., Garnick, M., Gomella, P., Handley, N., Hurwitz, M., Izes, J., Karnes, R.J., Lallas, C., Languino, L., Loeb, S., Lopez, A.M., Loughlin, K., Lu-Yao, G., Malkowicz, S.B., Mann, M., Mille, P., Miner, M., Morgan, T., Moreno, J., Mucci, L., Myers, R., Nielsen, S., O'Neil, B., Pinover, W., Pinto, P., Poage, W., Raj, G., Rebbeck, T., Ryan, C., Sandler, H., Schiewer, M., Scott, M., Szymaniak, B., Tester, W., Trabulsi, E., Vapiwala, N., Yu, E., Zeigler-Johnson, C., and Gomella, L.G. Implementation of Genetic Testing for Inherited Prostate Cancer: Philadelphia Prostate Cancer Consensus Conference 2019. *Journal of Clinical Oncology.* 2020 June 9. **[conference proceedings]**

58. Szymaniak, B.M., Facchini, L.A., Giri, V.N., Antonarakis, E.A., Beer, T.M., Carlo, M.I., Danila, D.C., Dhawan, M.,George, D., Graff, J.N., Gupta, S., Heath, E.I., Higano, C.S., Liu, G., Molina, A.M., Paller, C.J., Patnaik, A., Petrylak, D.P., Reichert, Z., Rettig, M.B., Ryan, C.J., Taplin, M.E., Whang, Y.E., Morgans, A.K.*, **Cheng, H.H.*,** McKay, R.R*. Practical Considerations and Challenges for Germline Genetic Testing in Prostate Cancer Patients: Recommendations from the Germline Genetics Working Group of the PCCTC. *JCO Oncol Pract.* 2020 Dec;16(12):811-819 **[review]** *(*co-senior author*)

59. Schweizer, M.T., **Cheng, H.H**., Nelson, P.S., Montgomery, R., Two steps forward and one step back for precision in prostate cancer treatment. *JCO.* 2020, Sept 8: JCO2001755. **[commentary]**

60. Carlson, A.S., Acevedo, R.I., Lim, D.M., Gulati, R., Gawne, A., Sokolova, A.O., **Cheng, H.H.,** Nelson, P.S., Montgomery, B., Yu, E.Y., Schweizer, M.T. (2020) Impact of mutations in homologous recombination repair genes on treatment outcomes for metastatic castration resistant prostate cancer. *PLoS ONE*. 2020, Sept 30. **[original work]**

61. Diamantopoulos, L.N., Holt, S.K., Khaki, A.R., Sekar, R.R., Gadzinski, A., Nyame, Y.A., Vakar-Lopez, F., Tretiakova, M., Psutka, S.P., Gore, J.L., Lin, D.W., Schade, G., Hsieh, A., Lee, J.K., Yezefski, T., Schweizer, M.T., **Cheng, H.H.,** Yu, E.Y., True, L.D., Montgomery, B., Grivas, P., Wright, J.L. Response to neoadjuvant chemotherapy and survival in micropapillary urothelial carcinoma: data from a tertiary referral center and Surveillance, Epidemiology, and End Results (SEER) program. *Clin Genitourin Cancer.* 2020, Oct 14. **[original work]**

62. Diamantopoulos, L.N., Sekar, R.R., Holt, S.K., Khaki, A.R., Miller, N.J., Gadzinski, A., Nyame, Y.A., Vakar-Lopez, F., Tretiakova, M., Psutka, S.P., Gore, J.L., Lin, D.W., Schade, G., Hsieh, A., Lee, J.K., Yezefski, T., Schweizer, M.T., **Cheng, H.H.,** Yu, E.Y., True, L.D., Montgomery, B., Grivas, P., Wright, J.L. Patterns and Timing of Perioperative Blood Transfusion and Association With Outcomes After Radical Cystectomy. *Urologic Oncology.* 2021 Feb 4. **[original work]**

63. Jensen, K., Konnick,, E.Q., Schweizer, M.T., Sokolova, A.O., Grivas, P., **Cheng, H.H.,** Klemfuss, N., Beightol, M., Yu, E.Y., Nelson, P.S., Montgomery, B., Pritchard, C.C. Clonal Hematopoiesis in DNA Repair Genes Substantially Interferes with Prostate Cancer Plasma Cell-free DNA Testing. *JAMA Oncology.* 2020, Nov 4. **[original work]**

64. Schaeffer, E., Srinivas, S., Antonarakis, E.S., Armstrong, A.J., Bekelman, J.E., **Cheng, H.H.**, D'Amico, A.V., Davis, B.J., Desai, N., Dorff, T., Eastham, J.A., Farrington, T.A., Gao, X., Horwitz, E.M., Ippolito, J.E., Kuettel, M.R., Lang, J.M., McKay, R., McKenney, J., Netto, G., Penson, D.F., Pow-Sang, J.M., Reiter, R., Richey, S., Roach, Iii M., Rosenfeld, S., Shabsigh, A., Spratt, D.E., Teply, B.A., Tward, J., Shead, D.A., Freedman-Cass, D.A. NCCN Guidelines Insights: Prostate Cancer, Version 1.2021. *J Natl Compr Canc Netw.* 2021 Feb 2;19(2):134-143. **[review]**

65. Ledet, E.M., Burgess, E.F., Sokolova, A.O., Jaeger, E.B., Hatton, W., Moses, M., Miller, P., Cotogno, P., Layton, J., Barata, P., Lewis, B., Nakazawa, M., Zhu, J., Dellinger, B., Elrefai, S., Nafissi., Egan, J.B., Shore, N., McKay, R., Bryce, A.H., **Cheng, H.H.**, Antonarakis, E.S., Sartor, O. Comparison of germline

mutations in African American and Caucasian men with metastatic prostate cancer**.** *The Prostate.* 2021, May. **[original work]**

66. **Cheng, H.H.** Molecular Subtyping in the Neoadjuvant Setting in Prostate Cancer—Envisioning the Possibilities. 2021, May 7. *European Urology* **[invited editorial]**

67. Loeb, S., Li, R., Sanchez Nolasco, T., Byrne, N., **Cheng, H.H.,** Becker, B., Leader, A., Giri, V.N. Barriers and Facilitators of Germline Genetic Evaluation for Prostate Cancer. 2021 May;81(7):433-439. *The Prostate* **[original work]**

68. Sokolova, A.O., Marshall, C.H., Lozano, R., Gulati, R., Ledet, E.M., De Sarkar, N., Grivas, P., Higano, C.S., Montgomery, B., Nelson, P.S., Olmos, D., Schweizer, M.T., Yezefski, T.A., Yu, E.Y., Paller, C.J., Sartor, O., Castro, E., Antonarakis, E.S., **Cheng, H.H.** Efficacy of systemic therapies in men with metastatic castration resistant prostate cancer harboring germline *ATM* versus *BRCA2* mutations. 2021 Sep 13. *The Prostate (*HHC corresponding author*) **[original work]**

69. Taza, F., Holler, A., Fu, W., Wang, H., Adra, N., ; Albany, C., Ashkar, R., **Cheng, H.H.,** Sokolova, A.O., Agarwal, N., Nussenzveig, R., Bryce, A., Nafissi, N. Barata, P., Sartor, A.O., Bastos, D., Smaletz, O., Berchuck, J., Taplin, M., Aggarwal, R., Sternberg, C., Vlachostergios, P.J., Alva, A.S., Su, C. Marshall, C.H., Antonarakis, E.S. Differential activity of PARP inhibitors in *BRCA1*- versus *BRCA2*-altered metastatic castration-resistant prostate cancer 2021, 1200-1220. *JCO Precision Oncology* **[original work]**

70. Martin, N.A., Tepper, J.E., Giri, V.N., Stinchcombe, T.E., **Cheng, H.H.,** Konnick, E.Q., Jayle, M., Selig, W. Adopting consensus terms for testing in precision medicine. 2021 Oct 6; *JCO Precision Oncology* **[commentary]**

71. Mostaghel, E.A., Yu, E.Y., Schweizer, M.T., **Cheng, H.H**., Marck, B.T., Sharifi, N., Matsumoto, A.M., Nelson, P.S., Montgomery, R.B., Association of Circulating and Intra-Tumor Adrenal Androgen Levels with Response to Abiraterone Acetate in Men with Castration Resistant Prostate Cancer. *2021 Nov 1;27(21):6001-6011. Clin Cancer Res* **[original work]**

72. Sokolova, A.O. and **Cheng, H.H.** Germline Testing in Prostate Cancer: When and Who to Test**.** 2021 Oct 20;35(10):645-653. *Oncology* **[review]**

73. **Cheng, H.H.*,** Maxwell, K.N.*, Powers, J.[*], Gulati, R., Ledet, E.M., Morrison, C., Le, A., Hausler, R., Stopfer, J., Hyman, S., Nemaur, A., Vagher, J., Greenberg, S., Naylor, L., Laurino, M., Konnick, E.Q., Al-Dubayan, S., Van Allen, E.M., Dubard-Gault, M., Montgomery, B., Nicolosi, P., Nussbaum, R.L., Maese, L.D., Schiffman, J.D., Garber, J.E., Lee, D., Schwartz, L.E., Nelson, P.S., Sartor, O., Walsh, M.F., Pritchard, C.C. Germline *TP53* pathogenic variants are associated with prostate cancer (***co-first author**, 2021 Dec 1;S0302-2838(21) 02139-4. *European Urology* **[original work]**

74. Weise, N., Shaya, J., Javier-Desloges, J., **Cheng, H.H.,** Madlensky, L., McKay, R.R. Disparities in Germline Testing Among Racial Minorities with Prostate Cancer. *2021 Nov 13;1-8. Prostate Cancer and Prostatic Diseases* **[review]**

75. Loeb, S., **Cheng. H.H.,** Leader, A., Gross, L., Byrne, N., Nolasco, T., Slater, E., Pieczonka, C., Gomella, L., Kelly, W.K., Trabulsi, E.J., Handley, N., Lallas, C.D., Chandrasekar, T., Mille, P., Mann, M., Mark, J.R., Brown, G., Chopra, S., Wasserman, J., Phillips, J., Somers, P., Giri, V.N. Technology-enhanced AcceleRation of Germline Evaluation for Therapy (TARGET): A randomized controlled trial of a pretest patient-driven webtool vs. genetic counseling for prostate cancer genetic testing. *2022 Jun 14;119:106821. Contemp Clin Trials.* **[original work]**

76. Symonds, L., Konnick, E., Vakar Lopez, F., **Cheng, H.H.,** Estey, E., Schweizer, M.T., Nelson, P.S., Pritchard, C.C., Montgomery, B. *BRCA2* Alterations in Neuroendocrine/Small Cell Carcinoma Prostate Cancer: A Case Series. 2022 Jul;6: PMID: 35834759; DOI: 10.1200/PO.22.00091 **[original work]**

77. Khan, H. and **Cheng, H.H.** Germline Genetics of Prostate Cancer. *2022 Aug;82 Suppl 1(Suppl 1):S3-S12. The Prostate* **[review]** *(*HHC corresponding author*)

78. Nyame, Y.A., Schraidt, J.A., Chakoian, M., Nissenberg, M.G., Luckenbaugh, A.N., Kirk,T.N., Wolff, E.M., **Cheng, H.H.,** Smith, A.B, Gore, J.L. A Patient-Centered Approach to Research Prioritization in Prostate Cancer. *2022 Aug;208(2):277-283. J Urology* **[original work]**

79. **Cheng, H.H.,** Sokolova, A.O., Gulati, R., Bowen, D., Knerr, S.A., Klemfuss, N., Alexander, K., Loesch, H., Grivas, P., Hsieh, A., Lee, J.K., Schweizer, M.T., Yezefski, T., Zhou, A., Yu, E.Y., Nelson, P.S., Montgomery, B., Internet-based Germline Genetic Testing for Men with Metastatic Prostate Cancer (*in press, JCO PO)* **[original work]**

80. Clark, N.M., Roberts, E.A., Federenko, C., Sun, Q., Dubard-Gault, M., Handford, C., Yung, R., **Cheng, H.H.,** Sham, J., Norquist, B., Flanagan, M.R. Genetic testing among patients with high-risk breast, ovarian, pancreatic, and prostate cancers. *2022 November; Annals of Surgical Oncology* https://doi.org/10.1245/s10434-022-12755-y [doi.org] **[original work]**

81. Su, C.T., Nizialek, E., Berchuck, J.E., Vlachostergios, P.J., Ashkar, R., Sokolova, A., Barata, P., Aggarwal, R.R., McKay, R.R., Agarwal, N., McClure, H., Nafissi, N., Bryce, A.H., Sartor, A.O., Sayegh, N., **Cheng, H.H.,** Adra, N., Sternberg, C., Taplin, M.E., Cieslik, M., Alva, A.S., Antonarakis, E.S., Differential responses to taxanes and PARP inhibitors in *ATM*- versus *BRCA2*-mutated metastatic castrate-resistant prostate cancer. *The Prostate, in press* **[original work]**

82. Seibert, T.M., Garraway, I.P., Plym, A., Mahal, B.A., Giri, V., Jacobs, M.F., **Cheng, H.H.,** Loeb, S., Helfand, B.T., Eeles, R.A., Morgan, T.M., Genetic risk prediction for prostate cancer: implications for early detection and prevention. *European Urology, in press* **[review]**

83. Gillessen S, Antonarakis E, Aparicio AM**,** Armstrong A, Attard G, Beer TM, Beltran H, Bjartell A, Blanchard P, Bossi A, Briganti A, Bristow RG, Bulbul M, Caffo O, Castellano D, Castro E, **Cheng HH**, Chi KN, Chowdhury S, Clarke CS, Clarke N, Daugaard G, Davis ID, de Bono J, de Santis M, Duran I, Eeles R, Efstathiou E, Efstathiou J, Ekeke ON, Evans CP, Fanti S, Feng FY, Fizazi K, Fonteyne V, Fossati N, Frydenberg M, George D, Gleave M, Gravis G, Halabi S, Heinrich D, Herrmann K, Higano C, Hofman MS, Horvath LG, Hussain M, James ND, Jereczek-Fossa BA, Jones R, Kanesvaran R, Kellokumpu-Lehtinen PL, Khauli RB, Klotz L, Kramer G, Leibowitz R, Logothetis C, Mahal B, Maluf F, Mateo J, Matheson D, Mehra N, Merseburger A, Morgans AK, Morris MJ, Mottet N, Mrabti H, Mukherji D, Murphy DG, Murthy V, Nguyen PL, Oh WK, Ost P, O'Sullivan JM, Padhani AR, Pezaro CJ, Poon DMC, Pritchard CC, Rabah DM, Rathkopf D, Reiter RE, Rubin M, Ryan CJ, Saad F, Sade JP, Sartor O, Scher HI, Sharifi N, Shore N, Skoneczna I, Small E, Smith M, Soule H, Spratt DE, Srinivas S, Sternberg CN, Steuber T, Suzuki H, Sweeney C, Sydes MR, Taplin ME, Tilki D, Tombal B, Türkeri L, Turco F, Uemura H, Uemura H, Ürün Y, Vale CL, van Oort I, Vapiwala N, Yamoah K, Ye D, Yu EY, Zapatero A , Zilli T, Omlin A. Management of patients with advanced prostate cancer: Report of the Advanced Prostate Cancer Consensus Conference (APCCC) 2022 *European Urology, in press* **[original work]**

84. Schweizer MT, Gulati R, Yezefski T, **Cheng HH**, Mostaghel E, Haffner MC, Patel RA, de Sarkar N, Ha G, Dumpit R, Woo B, Lin A, Panlasigui P, McDonald N, Lai M, Nega K, Hammond J, Grivas P, Hsieh A, Montgomery B, Nelson PS, Yu EY. Bipolar Androgen Therapy plus Olaparib in Men with Metastatic Castration-resistant Prostate Cancer (*in press)* **[original work]**

85. Makrakis, D., Wright, J.L., Roudier, M.P., Garcia, J., Vakar-Lopez, F., Porter, M.P., Wang, Y., Dash, A., Lin, D.W., Schade, G., Winters, B., Zhang, X., Nelson, P.S., Mostaghel, E., **Cheng, H.H.,** Schweizer, M.T., Holt, S.K., Gore, J.L., Yu, E.Y., Lam, H.M., Montgomery, B. A Phase 1/2 Study of Rapamycin and Cisplatin/Gemcitabine for Treatment of Patients With Muscle-Invasive Bladder Cancer (*in press, Clin Genitourinary Cancer)* **[original work]**

b) Collaborative Authorship: n/a

c) MedEDPortal or other peer reviewed curricula: n/a

d) Book Chapters:

1. **Cheng, H.H.** and Montgomery, R.B., (2015) Androgen Receptor Biology in Castration Resistant Prostate Cancer. Management of Castration Resistant Prostate Cancer, Current Clinical Urology, Springer Science and Business Media, NY.

2. **Cheng, H.H**. and Nelson, P.S. Genetic Risk Factors in Prostate Cancer. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on April 14, 2020)

3. Sokolova, A.O., Obeid, E., **Cheng, H.H.** Genetic Contribution to Metastatic Prostate Cancer. Urology Clinics N.A., Elsevier. (2021)

4. Szymaniak, B.M., Facchini, L.A., Kelsten, M.F., **Cheng, H.H.,** Morgans, A.K. Operationalizing Genetic Testing in the Care of Patients with Prostate Cancer. Urologic Oncology: Multidisciplinary Care for Patients, Springer. (2021)

e) Published Books, Videos, Software:

1. Dahut, W., **Cheng, H.H.** and Fadich, A. *The Future of Prostate Cancer Research and Treatment***.** National Cancer Institute YouTube Live, January 12, 2017. https://www.youtube.com/watch?cid=eb_govdel&v=2UTHKQuo2Ng

2. **Cheng, H.H.** *New Discoveries in Prostate Cancer.* Morning CME Webinar, January 17, 2017. MorningCME.com

f) Other Publications:

1. **Cheng, H.H.** and Linenberger, M. Into Thin Air: New Insights to the Role of Hypoxia-Inducible Factor in Cancer Biology and as a Target to Optimize Cell-Based Therapies. The Hematologist, Sept/Oct 2011.

2. **Cheng, H.H.** University of Washington Hematology/Oncology Fellows' Handbook. Author and editor of first edition, 2011.

3. **Cheng, H.H**. Expert contributor to patient educational website, 2015. (http://talkabouthealth.com/HeatherChengMDPhD)

4. **Cheng, H.H.,** Morgan, T.M., Dahut, W. Clinical Implications of Genetics: Expanding the Reach from Precision Therapy Opportunities for Prostate Cancer Patients to Prostate Cancer Screening for Genetically At-Risk Previvors. ASCO Genitourinary Symposium Expert Editorial, 2019.

5. **Cheng, H.** The Problem with Direct to Consumer Genetic Tests. Scientific American, March 10, 2020. https://blogs.scientificamerican.com/observations/the-problem-with-direct-to-consumer-genetic-tests/

g) Manuscripts Submitted:

1. Diamantopoulos, L.N., Khaki, A.R., Grivas, P., Gore, J.L., Schade, G., Hsieh, A., Lee, J.K., Yezefski, T., Yu, E.Y., Schweizer, M.T., **Cheng, H.H.,** Psutka, S.P., Lin, D.W., Tretiakova, M., Vakar-Lopez, F., Montgomery, B., Wright, J.L. Plasmacytoid urothelial carcinoma: a rare but aggressive bladder cancer variant with poor outcomes (*submitted)* **[original work]**

2. Sekar, R.R., Diamantopoulos, L.N., Bakaloudi, D.R., Khaki, A.R., Grivas, P., Winters, B.R., Vakar-Lopez, F., Tretiakova, M.S., Psutka, S.P., Holt, S.K., Gore, J.L., Lin, D.W., Schade, G.R., Hsieh, A.C., Lee, J.K., Yezefski, T., Schweizer, M.T., Cheng, H.H., Yu, E.Y., True, L.D., Montgomery, R.B., Wright, J.L. Sarcomatoid Urothelial Carcinoma is Associated with Limited Response to Neoadjuvant Chemotherapy and Poor Oncologic Outcomes after Radical Cystectomy (*submitted)* **[original work]**

3. Graff, J.N., Sokolova, A.O., Smith, C.E., Beer, T.M., Latour, E., Chen, Y., Bailey, S., Kreitner, D., Petreaca, D., Grivas, P., Schweizer, M.T., Higano, C.S., Alumkal, J.J., Vuky, J., Yu, E.Y., **Cheng, H.H.** A Phase I/II Trial of Concurrent Chemo-hormonal Therapy Using Enzalutamide and Cabazitaxel in Patients with Metastatic Castration Resistant Prostate Cancer. (*submitted)* **[original work]**

4. Zhao, J.L., Antonarakis, E.S., **Cheng, H.H.,** George, D., Aggarwal, R., Riedel, E., Sumiyoshi, T., Schonhoft, J., Mao, N., Haywood, S., Decker, B., Curley, T., Abida, A., Feng, F.Y., Knudsen, K., Carber, B., Lacouture, M.E., Wyatt, A., Rathkopf, D., Phase 1b Study of Enzalutamide plus CC-115, a dual mTORC1/2 and DNA-PK inhibitor, in Men with Metastatic Castration-Resistant Prostate Cancer. (*submitted)* [original work]

5. Lam, H., Ghali, F., Vakar-Lopez, F., Roudier, M., Garcia, J., Arora, S., **Cheng, H.,** Schweizer, M., Haffner, H., Lee, J., Yu, E., Grivas, P., Montgomery, B., Hsieh, A., and Wright, J. Metastatic bladder cancer expression and subcellular localization of Nectin-4 and Trop-2 in variant histology. (*submitted)* [original work]

6. Paller, C.J.*, Barata, P.C., Lorentz, J., Appleman, L.J., Armstrong, A.J., DeMarco, T.A., Dreicer, R., Elrod, J.B., Fleming, M., George, C., Heath, E.I., Hussain, M.H., Mao, S., McKay, R.M., Metwalli, A.R., Morgans, A., Stadler, W.M., Tran, C., Macario, N., Vinson, J., Green, R., **Cheng, H.H.*** PROMISE Registry: A Prostate Cancer Registry of Outcomes and Germline Mutations for Improved Survival and Treatment Effectiveness (*submitted)* **[original work]** *(*HHC co-senior author*)

7. Rencsok, E.M., Slopen, N., Autio, K., Morgans, A., McSwain, L., Barata, P., **Cheng, H.H.,** Dreicer, R., Heath, E., McKay, R., Pomerantz, M., Rathkopf, D., Tagawa, S., Whang, Y., Ragin, C., Folakemi O.T., George, D.J., Kantoff, P.W., Vinson, J., Villanti, P., Haneuse, S., Mucci, L.A. Quality of life in the year after diagnosis with advanced prostate cancer for Black and White individuals living in the US. (*submitted)* [original work]

8. Mita, A.C., Wei, Z., Gong, J., **Cheng, H.H**., Mitchell, E.P., Wright, J.J., Ivy, S.P., Wang, V., Gray, R.C., McShane, L.M., Rubinstein, L.V., Patton, D.R., Williams, P.M., Hamilton, S.R., Alva, A.S., Tricoli, J.V., Conley, B.A., Arteaga, C.L., Harris, L.N., O'Dwyer, P.J., Chen, A.P., Flaherty, K.T. Phase 2 Study of Erdafitinib in Patients with Tumors with *FGFR* Amplifications: Results from the NCI-MATCH ECOG-ACRIN Trial (EAY131) Sub-protocol K1. (*in preparation)* [original work]

h) Abstracts (last 5 years, 2017 to present**)**

1. True, L., Gulati, R., Lange, J., Tretiakov, M., Vakar-Lopez, F., Humphrey, P., Egevad, L., Hes, O., Antic, T., **Cheng, H.H.,** Montgomery, B., Nelson, P., Konnick, E., Schweizer, M., Pritchard, C.C. *Histological Patterns of Ductal Adenocarcinoma of Prostate Correlates with Mutations in DNA Repair Genes and May Aid in Selecting the Type of Systemic Therapy for Castration-Resistant Prostate Carcinoma.* 2017 United States & Canadian Academy of Pathology Annual Meeting (2017). Abstract #5047.

2. Schweizer, M.T., Haugk, K., **Cheng, H.H.,** Dumpit, R., Nelson, P.S., Montgomery, B., Plymate, S.R., Yu, E.Y. *Challenges in Enrolling to Metastatic Castration-Resistant Prostate Cancer (mCRPC) Studies that Require Androgen Receptor Splice Variant (AR-V) Positivity*. Genitourinary Cancers Symposium (2017). J Clin Oncol 35, 2017 (suppl 6S; abstract 264)

3. Shore, N.D., Heath, E.I., Whang, Y.E., Nordquist, L.T., **Cheng, H.H.**, Bhatt, K., Carroll, N., Mangrolia, D., Clasen, B., Kraynyak, K., Tagawa, S.T., Lin, J., Tutrone, R.F., Garcia, J.A., Lee, J., Yang, Z., Bagarazzi, M.L. *A clinical trial for the safety and immunogenicity of a DNA-based immunotherapy in men with biochemically (PSA) relapsed prostate cancer.* Genitourinary Cancers Symposium (2017). Abstract

4. Gill, D., Stenehjem, D., Hahn, A., **Cheng, H.**, Gupta, S., Alex, A., Patel, S., Kessler, E., Twardowski, P., Agarwal, N., *Association of time from definitive therapy (DT) to start of androgen deprivation therapy (ADT) for metastatic disease and survival outcomes in men with new metastatic hormone-sensitive prostate cancer (mHSPC).* Genitourinary Cancers Symposium (2017). J Clin Oncol 35, 2017 (suppl 6S; abstract 265)

5. Shore, N.D., Heath, E.I., Whang, Y.E., Nordquist, L.T., **Cheng, H.H.**, Bhatt, K., Carroll, N., Mangrolia, D., Clasen, B., Kraynyak, K., Tagawa, S.T., Lin, J., Tutrone, R.F., Garcia, J.A., Lee, J., Yang, Z., Bagarazzi, M.L. *Safety and Immunogenicity of a DNA-vaccine Immunotherapy in Men with Biochemically (PSA) Relapsed Prostate Cancer*. European Society of Medical Oncology Annual Meeting (2017) [Abstract 790PD, selected for oral poster discussion].

6. Schweizer, M.T., Gulati, R., **Cheng, H.H.,** de Sarkar, N., Yu, E.Y., Montgomery, B., Nelson, P.S., Pritchard, C.C. *Cell-free circulating tumor DNA is a reliable specimen for mutation profiling in prostate cancer patients with high-burden disease*. 24th Annual Prostate Cancer Foundation Scientific Retreat, Washington, D.C. (2017). [Abstract]

7. Mateo, J., **Cheng, H.H.,** Beltran, H., Dolling, D., Xu, W., Pritchard, C.C., Mossop, H., Rescigno, P., Perez-Lopez, R., Kolinsky, M., Balasapoulou, A., Carreira, S., Thorne, H., Montgomery, B., Sandhu, S., Rubin, M.A., Nelson, P., de Bono, J.S. *Clinical Outcomes of Prostate Cancer Patients with Germline DNA Repair Mutations: Follow-up From an International Study,* Genitourinary Cancers Symposium, San Francisco, CA (2018). [Abstract]

8. Montgomery, B., Russell, K., Liao, J.J., Ellis, W.J., **Cheng, H.H.**, Yu, E.Y., Mostaghel, E.M. *A Phase II Study of Neoadjuvant Degarelix on Prostatic Tissue Androgens Before Definitive Radiation,* Genitourinary Cancers Symposium, San Francisco, CA (2018). [Abstract]

9. Lim, D.M., Gulati, R., Aleshin-Guendel, S., **Cheng, H.H.,** Gawne, A., Wingate, J.T., Ruth, R., Etzioni, Yu, E.Y. *Prostate-Specific Antigen Recurrence Rates After Short Course Androgen Deprivation for Biochemical Recurrence of Prostate Cancer,* Genitourinary Cancers Symposium, San Francisco, CA (2018). [Abstract]

10. Lam, H., Vakar-Lopez, F., Hsieh, A.C., Winters, B., **Cheng, H.**, Schweizer, M., Yu, E.Y., Montgomery, B., Corey, E., Wright, J.L. *Bladder Cancer Rapid Autopsy: A mechanism for collecting metastatic tumor tissue and establishing xenograft models of metastatic disease,* Genitourinary Cancers Symposium, San Francisco, CA (2018). [Abstract]

11. **Cheng, H.H.,** Bowen, D., Klemfuss, N., Sievers, C.M., Kang, S.H., Zhou, A., Pritchard, C.C., Nelson, P.S., Montgomery, B., *The GENTleMEN Study: Genetic Testing for Men with Metastatic Prostate Cancer in Washington State and Beyond*, ASCO Annual Meeting, Chicago, IL (2018) [Abstract, poster]

12. Chae, Y.K., Vaklavas, C., **Cheng, H.H.,** Hong, F., Harris, L., Mitchell, E., Zwiebel, J., Rubinstein, L., McShane, L., Gray, R., Li, S., Ivy, P., Ansher, S., Hamilton, S., Williams, M., Patton, D., Tricoli, J., Arteaga, C., Conley. B., O'Dwyer, P., Chen, A., Flaherty, K., *Molecular Analysis for Therapy Choice (MATCH) Arm W: Phase II Study of AZD4547 in Patients with Tumors with Aberrations in the FGFR Pathway*, ASCO Annual Meeting, Chicago, IL (2018) [Abstract, oral presentation]

13. Yu, E.Y., Gulati, R., Aleshin-Guendel, S., **Cheng, H.H.,** Gawne, A., Wingate, J.T., Etzioni, R.,. Lim, D.M., *Undetectable PSA after short-course androgen deprivation therapy for biochemically-recurrent*

prostate cancer patients correlates with time to metastasis and prostate cancer-specific survival, ASCO Annual Meeting, Chicago, IL (2018) [Abstract]

14. Shore, N.D., Heath, E.I., Nordquist, L., **Cheng, H.H.,** Bhatt, K., Morrow, M., McMullan, T., Kraynyak, K., Lee, J., Sacchetta, B., Liu, L., Rosencranz, S., Tagawa, S.T., Parikh, R.A., Tutrone, R., Garcia, J., Y.Whang, Kelly, W., Csiki, I., Bagarazzi, M., *Safety and Immunogenicity of a DNA-vaccine for Immunotherapy in Biochemically Relapsed Prostate Cancer*, ASCO Annual Meeting, Chicago, IL (2018) [Abstract]

15. Rathkopf, D., Autio, K., Antonarakis, E., **Cheng, H.,** Arauz, G., Slack, A., Hullings, M., Scher, H.I., Feng, F., Knudsen, K. *Enzalutamide (ENZA) Plus CC-115 in Men with Metastatic Castration-Resistant Prostate Cancer (mCRPC): A Phase 1b Prostate Cancer Clinical Trials Consortium Study*, ASCO Annual Meeting, Chicago, IL (2018) [Abstract]

16. Schweizer, M.T., Antonarakis, E., Bismar, T.A., Guedes, L., **Cheng, H.H.,** Tretiakova, M.S., Vakar-Lopez, F., Klemfuss, N., Konnick, E.Q., Mostaghel, E.A., Hsieh, A.C., Nelson, P.S., Yu, E.Y., Montgomery, B., True, L.D., Epstein, J.I., Lotan, T.L., Pritchard, C.C. *Genomic Characterization of Ductal Adenocarcinoma of the Prostate*, ASCO Annual Meeting, Chicago, IL (2018) [Abstract, poster]

17. Naylor, L., Laurino, M., Sjoding, B., **Cheng, H.H.** *Prostate Cancer Genetics Clinic: First 16 Month Report of Establishing a Multidisciplinary Service*, European Society of Human Genetics, Milan, Italy (2018) [Abstract, poster]

18. Winters, B.R., De Sarkar, N., Arora, S., Bolouri, H., Lam, H., Vakar-Lopez, F., **Cheng, H.H.,** Schweizer, M.T., Yu, E.Y., Montgomery, B., Kollath, L., Grivas, P., Wright, J.L., Hsieh, A.C., *Metastatic upper tract urothelial carcinoma possesses a distinct genomic signature from lower tract urothelial carcinoma: Initial results from the University of Washington rapid autopsy program for urothelial carcinoma,* Western Section American Urological Association, Hawaii (2018) [Abstract]

19. Schweizer, M.T., Gulati, R., **Cheng, H.H.,** de Sarkar, N., Yu, E.Y., Montgomery, R.B., Nelson, P.S., Pritchard, C.C. *Cell-free Circulating Tumor DNA is a Reliable Specimen for Mutation Profiling in Prostate Cancer Patients with High-Burden Disease*. Fred Hutch Solid Tumor Translational Research Symposium (2018) [Abstract]

20. Shore, N.D., Heath, E.I., Nordquist, L., **Cheng, H.H.,** Bhatt, K., Morrow, M., McMullan, T., Kraynyak, K., Lee, J., Sacchetta, B., Liu, L., Rosencranz, S., Tagawa, S.T., Parikh, R.A., Tutrone, R., Garcia, J., Whang, Y., Kelly, W., Csiki, I., Bagarazzi, M., *Synthetic DNA Immunotherapy in Biochemically Relapsed Prostate Cancer*, European Society for Medical Oncology Annual Meeting (2018) [Abstract]

21. Labrecque, M.P., Brown, L.G., Coleman, I.M., True, L.D., Kollath, L., Lakely, B., Yang, Y.C.**,** Nguyen, H.M., Higano, C.S., Yu, E., **Cheng, H.H.,** Mostaghel, E., Montgomery, B., Schweizer, M., Hsieh, A., Corey, E., Nelson, P.S.**,** Morrissey, C. *Defining the molecular phenotypes of metastatic castration-resistant prostate cancer and their sensitivity to FGF pathway inhibition,* Prostate Cancer Foundation Scientific Retreat (2018) [Abstract]

22. Lam, H., Vakar-Lopez, F., **Cheng, H.H.,** Schweizer, M.T., Grivas, P., Yu, E.Y., Montgomery, B., Hsieh, A., Corey, E., Wright, J.L. *Bladder Cancer Rapid Autopsy: Emerging patient-derived xenograft models for metastatic diseases,* Society for Basic Urologic Research, Rancho, Mirage, CA (2018). [Abstract]

23. Sonpavde G., Agarwal N., Maughan B., Wei X., McGregor B., Kilbridge K., Lee R.J., Yu E.Y., Schweizer M.T., Montgomery B., **Cheng H.H.**, Hsieh A., Birhiray R., Gabrail N., Nemunaitis J., Rezazadeh A., Vanveldhuizen P., Vogelzang N., Heery C., Grivas P. *A Phase 2, Multicenter, Single-Arm Trial of CV301 plus Atezolizumab in Locally Advanced or Metastatic Urothelial Cancer*, Genitourinary Cancers Symposium, San Francisco, CA (2019). [Abstract]

24. Winters, B., De Sarkar, N., Arora, S., Bolouri, H., Vakar-Lopez, F., **Cheng, H.H.,** Yu, E.Y., Kollath, L., Grivas, P., McFerrin, L., Montgomery, B., Wright, J.L., Lam, H., Hsieh, A.C., *Distinct Genomic Hallmarks Exist Between Metastatic Upper and Lower Tract Urothelial Carcinoma*, Genitourinary Cancers Symposium, San Francisco, CA (2019). [Abstract]

25. Sokolova, A., **Cheng, H.H.**, Hintze, B., Kelley, M., Spector, N., Duffy, J., Lynch, J., Rettig, M., Montgomery, B., *The Veterans Health Administration Precision (VHA) Oncology Program for Advanced Prostate Cancer Patients: expanding tumor NGS opportunities to a broader patient population*, Genitourinary Cancers Symposium, San Francisco, CA (2019). [Abstract]

26. Winters, B., Ngo, S., Vakar-Lopez, F., Tretriakova, M., True, L., Dighe, M., Lee, J., Russell, K., Zeng, J., Liao, J.J., **Cheng, H.,** Montgomery, B., Schweizer, M., Hsieh, A., Yu, E., Schade, G., Gore, J., Lin, D., Wright, J. *Multi-specialty bladder cancer clinics can be associated with significant radiologic and pathologic diagnostic changes resulting in updated treatment recommendations: Results from a tertiary referral center*. American Urological Association Annual Meeting, Chicago, IL (2019). [Abstract]

27. Diamantopoulos, L.N., Khaki, A.R., Vakar Lopez, F., Tretiakova, M., Gore, J.L., Schade, G.R., Psutka, S., Hsieh, A., Lee, J., Yezefski, T., Schweizer, M.T., **Cheng, H.H.,** Yu, E.Y., Grivas, P., Montgomery, B., Wright, J.L. *Patient (pt) characteristics, treatment patterns, outcomes and prognostic factors in plasmacytoid urothelial carcinoma (PUC)* American Society for Clinical Oncology, Annual Meeting, Chicago, IL (2019). [Abstract]

28. Lynch, J., Lee, K.M., Pritchard, C., **Cheng, H**., Chantreau, C., Stoll, K., Meeks, J., Ball, D., Montgomery, B. *Clinically validating and returning MVP results to participants with mutation-positive metastatic prostate cancer*. Million Veteran Program Science Meeting, Philadelphia, PA (2019). [Abstract and oral presentation]

29. George, D., Mucci, L., Rathkopf, D., Chi, K., Zhang, T., Barata, P., **Cheng, H.,** Pomerantz, M., Dreicer, R., Alva, A., Ong, M., Heath, E., Enting, D., Whang, Y., Hotte, S., Bjartell, A., Fay, A., Omlin, A., Davis, I., Villanti, P., Vinson, J., Kantoff, P., *First 500 patients of IRONMAN: International Registry for Men with Advanced Prostate Cancer.* Prostate Cancer Foundation Annual Meeting, Carlsbad, CA (2019) [Abstract]

30. Mucci, L., Villanti, P., Vinson, J., Gold, T., Rathkopf, D., Chi, K., Zhang, T., Barata, P., **Cheng, H.,** Pomerantz, M., Dreicer, R., Alva, A., Ong, M., Heath, E., Enting, D., Whang, Y., Hotte, S., Bjartell, A., Fay, A., Morgans, A., Paich, K., McReynolds, J., George, D., Kantoff, P., *Patient Reported Outcomes among Men with Advanced Prostate Cancer: Results from the IRONMAN registry.* Prostate Cancer Foundation Annual Meeting, Carlsbad, CA (2019) [Abstract]

31. Ha, G., Doebley, A., Reichel, J., Hoge, A., **Cheng, H.H.,** Schweizer, M., Pritchard, C., Nelson, P. *Multi-omic profiling of circulating tumor DNA in patients with CRPC.* Prostate Cancer Foundation Annual Meeting, Carlsbad, CA (2019) [Abstract]

32. **Cheng, H.H.,** DeJong, M., Yu, E.Y., Rettig, M.B., Higano, C.S., Nelson, P.S., Pritchard, C.C., Montgomery, B. *A Pilot Study of Docetaxel and Carboplatin for treatment of patients with mCRPC containing biallelic inactivation of genes in the BRCA1/2 pathway*. Genitourinary Cancers Symposium, San Francisco, CA (2020). [Abstract]

33. Graff, J.N., **Cheng, H.H**., Vuky, J., Alumkal, J.J., Kreitner, D., Petreaca, D., Grivas, P., Schweizer, M.T., Higano, C.S., Yu, E.Y., Beer, T.M., *Phase II study of cabazitaxel (CAB) plus enzalutamide (ENZ) in metastatic castration resistant prostate cancer (mCRPC).* Genitourinary Cancers Symposium, San Francisco, CA (2020). [Abstract]

34. Graham, L.S., Montgomery, R.B., **Cheng, H.H.,** Yu, E.Y., Alva, A., Schweizer, M.T., *Mismatch Repair Deficiency in Metastatic Prostate Cancer (PC): Response to PD-1 Blockade and Standard Therapies.* Genitourinary Cancers Symposium, San Francisco, CA (2020). [Abstract]

35. Wong, R.L., Duong, M.T., Tangen, C.M., Agarwal, N., **Cheng, H.H.,** Vogelzang, N.J., Hussain, M., Thompson, I.M., Quinn, D.I., Yu, E.Y. *Final overall and progression-free survival outcomes from SWOG S0925, a randomized phase II study of androgen deprivation with cixutumumab versus androgen deprivation alone in patients with new metastatic hormone-sensitive prostate cancer.* Genitourinary Cancers Symposium, San Francisco, CA (2020). [Abstract]

36. Diamantopoulos, L.N., Khaki, A.R., Gadzinski, A., Winters, B.R., Vakar-Lopez, F., Tretiakova, M., Gore, J.L., Schade, G., Psutka, S.P., Hsieh, A., Lee, J.K., Yezefski, T., Schweizer, M.T., **Cheng, H.H.,** Yu, E.Y., Lin, D.W., Montgomery, B., Grivas, P., Wright, J.L. Micropapillary Urothelial Carcinoma: a Comparative Analysis of Oncologic Outcomes Compared to Conventional Urothelial Carcinoma. Genitourinary Cancers Symposium, San Francisco, CA (2020). [Abstract]

37. Diamantopoulos, L.N., Sekar, R.R., Khaki, A.R., Winters, B.R., Vakar-Lopez, F., Tretiakova, M., Gore, J.L., Schade, G., Psutka, S.P., Hsieh, A., Lee, J.K., Yezefski, T., Schweizer, M.T., **Cheng, H.H.,** Yu, E.Y., Lin, D.W., Montgomery, B., Grivas, P., Wright, J.L. *Sarcomatoid Urothelial Cancer (SUC): An Aggressive Variant with A Unique Pattern of Recurrence.* Genitourinary Cancers Symposium, San Francisco, CA (2020). [Abstract]

38. Sokolova, A.O., Marshall, C.H., Lozano, R., Grivas, P., Higano, C.S., Montgomery, B., Nelson, P.S., Schweizer, M.T., Yezefski, T.A., Yu, E.Y., Paller, C.J., Castro, E., Antonarakis, E.A., **Cheng, H.H.,** *Clinical characteristics and treatment response of prostate cancer patients with germline ATM mutations.* Genitourinary Cancers Symposium, San Francisco, CA (2020). [Abstract]

39. Psutka, S.P., Ngo, S., Diamantopoulos, L., Maldonado, R., O'Malley, R., Laidlaw, G.L., Fintelmann, F., Holt, H., Gore, J.L., Schade, G.R., Lin, D.W., Grivas, P., Montgomery, B., Hsieh, A.C., **Cheng, H.H.,** Yezefski, T.A., Schweizer, M.T., Yu, E.Y., Wright, J.L. *Associations between baseline Skeletal Muscle Index, Neoadjuvant Chemotherapy-Associated Severe Adverse Events and 90-day Post-Radical Cystectomy Complication.* American Urological Associate, Washington, DC (2020). [Abstract]

40. Psutka, S.P., Ngo, S., Diamantopoulos, L., Maldonado, R., O'Malley, R., Laidlaw, G.L., Fintelmann, F., Holt, H., Gore, J.L., Schade, G.R., Lin, D.W., Grivas, P., Montgomery, B., Hsieh, A.C., **Cheng, H.H.,** Yezefski, T.A., Schweizer, M.T., Yu, E.Y., Wright, J.L. *Associations between baseline Skeletal Muscle Index, Fat Mass Index, and Cancer-Specific Mortality following Neoadjuvant Chemotherapy and Radical Cystectomy for Bladder Cancer.* American Urological Associate, Washington, DC (2020). [Abstract]

41. Pouv, D.L., Sokolova, A.O., **Cheng., H.H**. Seattle Cancer Care Alliance Prostate Cancer Genetics Clinic: Germline Genetic Testing in Practice and its Implications for Precision Therapy. Western Medical Research Conference, Carmel, CA (2020). [Abstract]

42. Facchini, L., Naylor, L., Sjoding, B., Laurino, M., Handford. C., Lally, E., **Cheng, H.H.,** *Seattle Cancer Care Alliance's Prostate Cancer Genetics Clinic: A report of 125 patients between 2017-2019*. Hereditary Breast and Ovarian Cancer Symposium, Montreal, Ontario. (2020) [Abstract]

43. Diamantopoulos, L.N., Sekar, R.R., Khaki, A.R., Winters, B.R., Vakar-Lopez, F., Tretiakova, M., Gore, J.L., Schade, G.R., Psutka, S.P., Hsieh, A., Lee, J.K., Yezefski, T., Schweizer, M.T., **Cheng, H.H.,** Yu, E.Y., Lin, D.W., Montgomery, B., Grivas, P., Wright, J.L. *Association of Perioperative Blood Transfusion (PBT) With Post-Operative Outcomes In Patients (Pts) Undergoing Radical Cystectomy (RC) For Bladder Cancer (BC).* American Society for Clinical Oncology Annual Meeting, Chicago, CA (2020). [Abstract]

44. Diamantopoulos, L.N., Ngo, S., Maldonado, R., O'Malley, R., Laidlaw, G., Fintelmann, F.J., Holt, S.K., Gore, J.L, Schade, G., Lin, D.W., Grivas, P., Montgomery, B., Hsieh, A.C., **Cheng, H.H.,** Yezefski, T , Schweizer, M.T., Yu, E.Y., Wright, J.L., Psutka, S.P. *Associations between Baseline Body Composition and Cancer-Specific Mortality following Neoadjuvant Chemotherapy and Radical Cystectomy for*

Bladder Cancer. American Society for Clinical Oncology Annual Meeting, Chicago, CA (2020). [Abstract]

45. Ledet, E.M., Jaeger, E., Hatton, W., Moses, M.W., Sokolova, A.O., Nakazawa, M., Zhu, J., Dellinger, B., Elrefai, S., McKay, R.R., **Cheng, H.H.,** Burgess, E.F., Antonarakis, E.S., Sartor, A.O. *Comparison of germline mutations in African American and Caucasian men with metastatic prostate cancer*. American Society for Clinical Oncology Annual Meeting, Chicago, CA (2020). [Abstract]

46. Geisler, A., Barrios, D.M., Lacouture, M.E., Antonarakis, E.S., George, D.J., **Cheng, H.H**., Aggarwal, R.R., Rathkopf, D.E., *CC-115 Treatment-Related Rash in Castration-Resistant Prostate Cancer*. American Society for Clinical Oncology Annual Meeting, Chicago, CA (2020). [Abstract]

47. Ngo, S. Diamantopoulos, L.N., Maldonado, R., O'Malley, R.B., Laidlaw, G., Fintelmann, F.J., Holt, S.K., Gore, J.L., Schade, G.R., Lin, D.W., Grivas, P., Montgomery, R.B., Hsieh, A.C., **Cheng, H.H**., Yezefski, T., Schweizer, M.T., Yu, E.Y., Wright, J.L., Psutka, S.P., *Skeletal Muscle Index and Adverse Events during a Bladder Cancer Treatment Episode*. American Society for Clinical Oncology Annual Meeting, Chicago, CA (2020). [Abstract]

48. Sekar, R.R., Diamantopoulos, L.N., Khaki, A.R., Vakar-Lopez, F., Tretiakova, M., Psutka, S.P., Hold, S.K., Gore, J.L., Schade, G.R., Lin, D.W., Hsieh, A., Lee, J.K., Yezefski, T., Schweizer, M.T., **Cheng, H.H.,** Yu, E.Y., True, L.D., Montgomery, B., Grivas, P., Wright, J.L. *Sarcomatoid Urothelial Carcinoma: Oncologic Outcomes From A Tertiary Center And SEER-Medicare Data.* American Society for Clinical Oncology Annual Meeting, Chicago, CA (2020). [Abstract]

49. Sokolova, A.O., Miyamoto, A.N., Pouv, D.L., **Cheng, H.H.,** Montgomery, R.B. *Implementation of Systematic Germline Genetic Testing (GT) for Metastatic Prostate Cancer (mPC) Patients at the Puget Sound VA Prostate Oncology Clinic.* American Society for Clinical Oncology Annual Meeting, Chicago, CA (2020). [Poster abstract]

50. Wong, R.L., Lin, D.W., Pritchard, C.C., Nelson, P.S., Stanford, J.L., **Cheng, H.H.** *Genetic Information to Inform Treatment and Screening (GIFTS) Study for Prostate Cancer: Characterizing Germline DNA Alterations in Men with Metastatic Prostate Cancer and their First-Degree Male Relatives.* European Society for Medical Oncology, virtual (2020). [Poster abstract]

51. Loeb, S., Thakker, S., Falge, E., Taneja, S., Byrne, N., Walter, D., Katz, M., Wong, R., Leader, A., Selvan, P., Rose, M., Joy, M., **Cheng, H.H.,** Massey, P., and Giri, V.N. *Twitter Discussions about Genetic Testing and BRCA Awareness in the Context of Prostate Cancer and Breast Cancer.* Prostate Cancer Foundation Annual Retreat, virtual (2020). [Poster abstract]

52. Rathkopf, D., Chi, K.N., Olmos, D., **Cheng, H.H.,** Agarwal, N., Graff, J., Sandhu, S., Hayreh, V., Lopez-Gitlitz, A., Francis, P., Attard, G. *AMPLITUDE: A Study of Niraparib (Nira) in Combination With Abiraterone Acetate and Prednisone (AAP) Versus AAP for the Treatment of Patients With Deleterious Germline or Somatic Homologous Recombination Repair (HRR) Gene-mutated Metastatic Castration-sensitive Prostate Cancer*. Genitourinary Cancers Symposium, San Francisco, CA (2021). [Abstract]

53. Wong, R.L., **Cheng, H.H.,** Holt, S.K., Conrad, N., Fernandez, S., Sahoo, R., Bauer, Z., Toulouse, A.E., Grivas, P., Yezefski, T., Russell, K.J., Wright, J.L, Schweizer, M.T., Montgomery, R.B., Lee, J.H., Chen, D.L., Zeng, J., Lin, D.W., Yu, E.Y. *Use of Fluciclovine PET/CT (FluPET) for Prostate Cancer: Initial Results from a Prospective Registry at the University of Washington/Seattle Cancer Care Alliance.* Genitourinary Cancers Symposium, San Francisco, CA (2021). [Abstract]

54. Loeb, S., Li, R., Sanchez Nolasco, T., Byrne, N., **Cheng, H.H.,** Leader, A., Giri, V., *Barriers and Facilitators of Germline Genetic Evaluation for Prostate Cancer*. Genitourinary Cancers Symposium, San Francisco, CA (2021). [Abstract]

55. Taza, F., Holler, A., Adra, N., Albany, C., Ashkar, R., **Cheng, H.H.,** Sokolova, A.O., Agarwal, N., Nussenzveig, R., Bryce, A., Nafissi, N., Barata, P., Sartor, O., Bastos, D., Smaletz, O., Berchuck, J., Taplin, M., Aggarwal, R., Sternberg, C., Vlachostergios, P.J., Alva, A.S., Su, C., Marshall, C.H., Antonarakis, E.S. *Differential activity of PARP inhibitors in BRCA1- vs BRCA2-altered metastatic castration-resistant prostate cancer (mCRPC).* Genitourinary Cancers Symposium, San Francisco, CA (2021). [Abstract]

56. Karzai, F., Couvillon, A., McKinney, Y., Lee-Wisdom, K., Choyke, P.L., Giri, V.N., Morgan, T.M., **Cheng, H.H**., Merino, M.J., Pinto, P.A., Turkbey, B., Dahut, W.L., *A Natural History Study of Men with High-Risk Genetics for Prostate Cancer (PCa) Using Multiparametric MRI (mpMRI).* American Association for Cancer Research Annual Meeting, Washington, D.C. (2021). [Abstract]

57. Rathkopf, D.E., Chi, K.N., Olmos, D., **Cheng, H.H.,** Agarwal, N., Graff, J.N., Sandhu, S.K., Hayreh, V., Lopez-Gitlitz, A., St. John, P., Attard, G., *AMPLITUDE: A Study of Niraparib in Combination With Abiraterone Acetate Plus Prednisone (AAP) vs AAP Alone for the Treatment of Metastatic Castration-Sensitive Prostate Cancer (mCSPC) in Patients With Deleterious Germline orSomatic Homologous Recombination Repair (HRR) Gene Alterations.* American Society for Clinical Oncology Annual Meeting, Chicago, CA (2021). [Abstract]

58. Zhao, J.L., Antonarakis, E.S., **Cheng, H.H.,** George, D.G., Aggarwal, R.A., Abida, W., Decker, B., Curley, T., Schonhoft, J., Haywood, S., Riedel, E., Carver, B., Wyatt, A., Feng, F.Y., Knudsen, K., Rathkopf, D. *A Phase 1b Study of Enzalutamide (Enza) plus CC-115 in Men with Metastatic Castration-Resistant Prostate Cancer (mCRPC).* American Society for Clinical Oncology Annual Meeting, Chicago, CA (2021). [Abstract]

59. Wong, R.L., Holt, S.K., Zeng, J., Graham, L., Kang, R., Conrad, N., Toulouse, A.E., Fernandez, S., Bauer, Z., Lai, M.Y., Yezefski, T., Wright, J.L, Weg, E.S., Hsieh, A.C., **Cheng, H.H.,** Lee, J.H., Chen, D.L., Lin, D.W., Yu, E.Y. *The fluciclovine (FACBC) PET/CT site-directed therapy of oligometastatic prostate cancer (Flu-BLAST-PC) trial.* American Society for Clinical Oncology Annual Meeting, Chicago, CA (2021). [Abstract]

60. Su, C.T., Nizialak, E., Berchuck, J.E., Vlachostergios, P., Ashkar, R., Sokolova, A.O., Barata, P., Aggarwal, R., McClure, H., Sartor, O., **Cheng, H.H.,** Adra, N., Sternberg, C.N., Taplin, M.E., Cieslik, M., Antonarakis, E., Alva, A. *Differential responses to taxanes and PARP inhibitors (PARPi) in ATM- versus BRCA2-mutated metastatic castrate-resistant prostate cancer (mCRPC) patients (pts)*. American Society for Clinical Oncology Annual Meeting, Chicago, CA (2021). [Abstract]

61. Giri, V.N., Walker, A., Gross, L., Fisher, C., **Cheng, H.H.,** Loeb, S. *HELIX: Development and Testing of New Digital Tool to Facilitate Guideline-Concordant Prostate Cancer Genetic Testing in Clinical Practice.* American Urological Association (2021). [Abstract]

62. Maldonado, R., Jan Marquardt, J., Fintelmann, F., O'Malley, R., Holt, S., Ngo, S., Diamantopoulos, L., Laidlaw, G., Schade, G., Lin, D.W., Wright, J.L., Gore, J.L., Nyame, Y., Grivas, P., Yu, E.Y., Montgomery, B., Hsieh, A., Yezefski, T., Schweizer, M., **Cheng, H.H.**, Psutka, S.P. *Change in Skeletal Muscle (SMI), Subcutaneous (SFI) and Visceral Fat Indices (SFI) with Neoadjuvant Chemotherapy (NAC) in patients with Muscle Invasive Bladder Cancer (MIBC): Associations with Adverse Events (AEs) and Oncologic Outcomes.* American Urological Association (2021). [Abstract]

63. Szymaniak, B.M., Facchini, L.A., **Cheng, H.H.,** Morgans, A.K., *Integrating Genetic Counseling and Testing into Genitourinary (GU) Oncology & Urology Clinics.* BRCA Conference (2021). [Abstract]

64. Couvillon, A., Karzai, F., Choyke, P.L., Giri, V.N., Morgan, T.M., **Cheng, H.H.,** Kesserwan, C., Merino, M.J., Pinto, P.A., Turkbey, B., Dahut, W.L., *Inherited Risk for Prostate Cancer: How to Follow and Image the Natural History of Men with High-Risk Genetics*. BRCA Conference (2021). [Abstract]

65. Schweizer, M.T., Roman Gulati, R., Yezefski, T., **Cheng, H.H.,** Sievers, C., Ruth Dumpit, Alexander, K., McDonald, N., Lai, M., Nega, K., Hammond, J., Grivas, P., Hsieh, A., Montgomery, B., Nelson, P.S., Yu, E.Y. Bipolar Androgen Therapy (BAT) plus Olaparib in Men with Metastatic Castration-resistant Prostate Cancer (mCRPC). European Society of Medical Oncology (2021). [Abstract]

66. **Cheng, H.H.**, Powers, J., Gulati, R., Le, A., Ledet, E., Van Allen, E., Vijai, J., Nicolosi, P., Nussbaum, R.L., Garber, J.E., Offit, K., Schiffman, J., Sartor, O., Nelson, P.S., Walsh, M.F., Pritchard, C.C., Maxwell, K.N. *TP53* variants are associated with an increased risk of prostate cancer. American Society of Human Genetics (2021). [Poster Abstract]

67. Maldonado, R., Marquardt, J.P., Fintelmann, F.J., O'Malley, R., Holt, S.K., Ngo, S., Diamantopoulos, L., Laidlaw, G., Schade, G.R., Lin, D.W., Wright, J.L., Gore, J.L., Nyame, Y., Grivas, P., Yu, E.Y., Montgomery, B., Hsieh, A.C., Yezefski, T.A., Schweizer, M., **Cheng, H.H.,** Psutka, S.P. Changes in Body Composition During Platinum-based Neoadjuvant Chemotherapy (NAC) Prior to Radical Cystectomy (RC and Association with Outcomes. Society for Urologic Oncology (2021). [Abstract]

68. Zhao, J.L., Antonarakis, E.S., **Cheng, H.H.,** George, D.G., Aggarwal, R.A., Abida, W., Decker, B., Curley, T., Schonhoft, J., Anderson, A., Haywood, S., Riedel, E., Carver, B., Wyatt, A., Feng, F.Y., Knudsen, K., Rathkopf, D. *A Phase 1b Study of Enzalutamide (Enza) plus CC-115 in Men with Metastatic Castration-Resistant Prostate Cancer (mCRPC).* European Society of Medical Oncology (2021). [Abstract]

69. Mita, A.C., Mayer, I., Conley, B., Harris, L., Arteago, C., Maican, T., **Cheng.,H.H.** *Erdafitinib in patients with tumors harboring FGFR gene mutations or fusions: results from the NCI-MATCH arm K2 trial.* AACR-NCI-EORTC Molecular Targets and Cancer Therapeutics Virtual Conference (2021). [Abstract]

70. Selvan, P., Leader, A., Hunter, A., Massey, P., **Cheng, H.H.,** Loeb, S., Giri, V.N., *Assessing the Impact of Messaging about Prostate Cancer and Genetics on Facebook*. Prostate Cancer Foundation Annual Retreat, virtual (2021). [Poster abstract]

71. Sokolova, A.O., Gulati, R., **Cheng, H.H.,** Beer, T., Graff, J.N., Vuky, J., Yezefski, T., Grivas, P., Yu, E.Y., Schweizer, M.T. *Trial in progress: Durvalumab and Olaparib for the Treatment of Prostate Cancer in Men Predicted to Have a High Neoantigen Load.* Genitourinary Cancers Symposium, San Francisco, CA (2022). [Abstract]

72. Giri, V.N., **Cheng, H.H.,** Paller, C., Weg, E., Johnson, J., Gross, L., Russo, J., Loeb, S., *Virtual Genetics Board for Enhancing Knowledge and Practice of Prostate Cancer Genetic Testing: The ENGAGEMENT Study.* Genitourinary Cancers Symposium, San Francisco, CA (2022). [Poster Abstract]

73. Paller, C.J., Lorentz, J., DeMarco, T.A., Stadler, W.M., Armstrong, A.J., Taplin, M., Hussain, M.H., Pili, R., Mao, S., Elrod, J.B., Sokolova, A.O., Heath, E.I., McKay, R.M., Vinson, J., Tran, C., Macario, N., Cook, A., Chiang, J., **Cheng, H.H.** *PROMISE Registry: A Prostate Cancer Registry of Outcomes and Germline Mutations for Improved Survival and Treatment Effectiveness.* Genitourinary Cancers Symposium, San Francisco, CA (2022). [Abstract]

74. Clark, N.M., Roberts, E.A., Fedorenko, C., Sun, Q., Dubard-Gault, M., Handford, C., Yung, R., **Cheng, H.**, Norquist, B., Flanagan, M.R. *Guideline concordant genetic testing in patients with breast, ovarian, pancreatic and prostate cancer.* International Conference on Surgical Cancer Care, Dallas, TX (2022) [e-poster, Abstract]

75. Makrakis, D., Roudier, M.P., Wang, Y., Vakar-Lopez, F., Garcia, J., Dash, A., Lin, D., Schade, G., Mostaghel, E.M., **Cheng, H.H.,** Schweizer, M.T., Gore, J.L., Yu, E.Y., Lam, H.M., Wright, J.L., Montgomery, B. *A Phase 1/2 Study of Rapamycin and Cisplatin/Gemcitabine for Treatment of Patients With Bladder Cancer (NCT01938573).* American Urological Association (2022). [Abstract]

76. Garcia, J., Vakar-Lopez, F., Roudier, M., Grivas, P., Yu, E.Y., **Cheng, H.H.,** Schweizer, M.T., Haffner, M., Lee, J.K., Corey, E., Montgomery, B., Hsieh, A.C., Wright, J.L., Lam, H. *An update on the Urothelial Cancer Rapid Autopsy Program: Biospecimens and Patient-derived Preclinical Models.* American Urological Association (2022). [Abstract]

77. Noonavath, M., Muney, K., Marquandt, J.P., Fintelmann, F.J., O'Malley, R., Holt, S.K., Dwyer, E., Maldonado, R., Diamantopoulos, L., Makrakis, D., Laidlaw, G., Schade, G.R., Lin, D.E., Wright, J.L., Nyame, Y., Grivas, P., Yu, E.Y., Montgomery, B., Hsieh, A.C., Yezefski, T.A., Schweizer, M.T., **Cheng, H.H.,** Psutka, S.P. *Skeletal Muscle Gauge: A Novel Assessment of Muscle Mass and Quality: Associations with Outcomes Following Radical Cystectomy for Bladder Cancer.* American Urological Association (2022). [Abstract]

78. Gulhane, A. Lin, D., Dash, A., Nyame, Y., Schade, G., Wright, J., Chen, J., Liao, J., Wallner, K., Weg, E., **Cheng, H.H**., Hawley, J., Montgomery, B., Nelson, P.S., Schweizer, M.T., Yu, E.Y., Chen, D.L. *[^{68}Ga]-PSMA-11 clarifies equivocal lesions on conventional imaging and affects management for men with prostate cancer*. Society of Nuclear Medicine and Molecular Imaging Annual Meeting (2022). [Abstract]

79. Wong, R.L., **Cheng, H.H.,** Fann, J.R., Hnida, J., Chakoian, M., Schenker, Y., Yu, E.Y., Gore, J.L. *Longitudinal Screening for Depression and Anxiety in Prostate Cancer and Association with Disease and Treatment Factors*. American Society of Clinical Oncology Annual Meeting (2022). [Abstract]

80. Khan, H.M., Wong, R.L., Darst, B.F., Pritchard, C.C., Nelson, P.S., Stanford, J.L., Lin, D.W., **Cheng, H.H.** *Cancer Registry-Based Recruitment of Men with Incident Metastatic Prostate Cancer and their First-Degree Male Relatives for Germline Genetic Testing: Genetic Information to Inform Treatment and Screening (GIFTS) Study*. American Society of Clinical Oncology Annual Meeting (2022). [Oral Abstract Presentation] *(*HHC senior author)*

81. Gulhane, A., Talukder, R., Dash, A., Ellis, W., Nyame, Y.A., Schade, G., Wright, J.L., Apisarnthanarax, S., Chen, J., Liao, J.J., Wallner, K., Weg, E.S., **Cheng, H.H.,** Grivas, P., Hawley, J., Hsieh, A.C., Lee, J.K., Montgomery, B., Nelson, P.S., Schweizer, M.T., Yezefski, Y., Yu, E.Y., Lin, D.W., Chen, D.L. *Clinical Impact of PSMA PET in patients with biochemical recurrence of prostate cancer after local definitive therapy.* American Society of Clinical Oncology Annual Meeting (2022). [Abstract]

82. Liao, J.J., Mostaghel, E.A., Russell, K.J., Dalkin, B.L., Ellis, W.J., Lin, D., Wright, J., Schade, G., Nyame, Y., Yu, E.Y., Nelson, P., Grivas, P., Schweizer, M.T., **Cheng, H.H.,** Yezefski, T., Hawley, J.E.., Chen, J.J., Weg, E., Nguyen, M., Montgomery, B., *Abiraterone, Androgen Deprivation Therapy, and Radiotherapy for Localized High Risk and Intermediate Risk Prostate Cancer: Long-term follow up of the RAD1 Phase 2 trial.* American Society of Radiation Oncology, Annual Meeting (2022). [Abstract]

83. Garcia, J., Vakar-Lopez, F., Roudier, M., Grivas, P., Yu, E.Y., **Cheng, H.H.,** Schweizer, M.T., Haffner, M., Lee, J.K., Corey, E., Montgomery, B., Hsieh, A.C., Wright, J.L., Lam, H. *Bladder Cancer Rapid Autopsy Program provides a critical resource for the biological study of advanced bladder cancer.* American Urological Association (2022). [Abstract]

84. Gulhane, A., Talukder, R., Dash, A., Ellis, W., Nyame, Y.A., Schade, G., Wright, J.L., Apisarnthanarax, S., Chen, J., Liao, J.J., Wallner, K., Weg, E.S., **Cheng, H.H.,** Grivas, P., Hawley, J., Hsieh, A.C., Lee, J.K., Montgomery, B., Nelson, P.S., Schweizer, M.T., Yezefski, Y., Yu, E.Y., Lin, D.W., Chen, D.L. *Utility of PSMA PET for Initial Staging of Prostate Cancer.* Radiological Society of North America (2022). [Abstract]

85. Lorentz, J., Appleman, L., Armstrong, A.J., Barata, P., DeMarco, T.A., Dreicer, R., Elrod, J.B., Fleming, M., George, C., Heath, E.I., Hussain, M.A., Mao, S., McKay, R.R., Metwalli, A., Morgans, A., Orton, M., Pili, R., Saraiya, B., Sigmond, J., Sokolova, A.O., Stadler, W.M., Tran, C., Macario, N., Vinson, J., Green, R., Paller, C.J., **Cheng, H.H.** *Utilization of a decentralized national genetic registry to address*

informational needs caused by expanded testing recommendations and recently approved treatments for prostate cancer: the PROMISE Registry. National Society for Genetic Counseling (2022) [Abstract]

86. Wong, R.L., **Cheng, H.H.,** Fann, J.R., Hnida, J., Chakoian, M., Schenker, Y., Yu, E.Y., Gore, J.L. *Depression Screening in Prostate Cancer and Use of Supportive Care Services.* ASCO Quality Care Symposium (2022) [Abstract]

87. Rathkopf, D.E., Chi, K.N., Olmos, D., **Cheng, H.H.,** Agarwal, N., Graff, J.N., Sandu, S.K., Kim, W., Lopez-Gitlitz, Francis, P.S., Attard, G., *AMPLITUDE: Niraparib and Abiraterone Acetate Plus Prednisone to Treat Patients with Metastatic Castration Sensitive Prostate Cancer and Deleterious Germline or Somatic Homologous Recombination Repair Gene Alterations*. Society for Urology Oncology (2022) [Abstract]

88. Paller, C.J.*, Barata, P.C., Lorentz, J., Appleman, L.J., Armstrong, A.J., DeMarco, T.A., Dreicer, R., Elrod, J.B., Fleming, M., George, C., Heath, E.I., Hussain, M.H., Mao, S., McKay, R.M., Metwalli, A.R., Morgans, A., Stadler, W.M., Tran, C., Macario, N., Vinson, J., Green, R., **Cheng, H.H.*** *PROMISE Registry: A Prostate Cancer Registry of Outcomes and Germline Mutations for Improved Survival and Treatment Effectiveness*. Prostate Cancer Foundation Annual Retreat (2022). [Poster abstract]

89. Couvillon, A., Turkbey, B., Choyke, P.L., Lee-Wisdom, K., McKinney, Y., Sidlow, R., Mullane, M., Giri, V.N., Morgan, T.M., **Cheng, H.H.,** Merino, M.J., Figg, W., Pinto, P.A., Dahut, W.L., Karzai, F. *Inherited Risk for Prostate Cancer (PCa): Following the Natural History of Men with High-Risk Genetics using Multiparametric MRI (mpMRI).* ASCO Genitourinary Cancer Symposium (2023). [Abstract]

90. Giri, V.N., Gross, L., Hartman, R., Reader, A.E., Whang, Y.E., Couvillon, A., **Cheng, H.H.,** Paller, C.J., Loeb, S., Karsh, L.I., Friedman, S., Beer, T.M., Keith, S. *Factors Impacting Men's Experience with Prostate Cancer Germline Testing: Results from PROGRESS Registry.* ASCO Genitourinary Cancer Symposium (2023). [Abstract]

91. Koehne, E., Vakar-Lopez, F., Roudier, M., Garcia, J., Arora, S., **Cheng. H.H.,** Schweizer, M.T., Haffner, M., Lee, J.K., Yu, E.Y., Grivas, P., Montgomery, B., Hsieh, A., Wright, J.L., Lam, H. *Molecular Characterization of Plasmacytoid Urothelial Carcinoma Metastases from Rapid Autopsy.* American Urological Association (2023). [Abstract]

92. Erickson, M.S., Scherzer, Z., Toderas, L., Schweizer, M., Yu, E.Y., **Cheng, H.H.,** Yezefski, T.A., Hsieh, A.T., Montgomery, B., Nelson, P.S., Hawley, J., Chen, D.L., Iravani, A., *Best Practices for Limiting Treatment Cancellations of Lutetium-177 PSMA-617*. Society of Nuclear Medicine and Molecular Imaging Annual Meeting (2023). [Abstract]

18. Invited Talks, including CME presentations

a. National/International Invited Lectures

1. 12/2002: *Identifying the Requirements and Mechanisms of FeLV-T Entry*. **2002 International Workshop on Retroviral Pathogenesis**, Indian Wells, CA [invited lecture]

2. 05/2003: *Determinants of Receptor Specificity for Feline Leukemia Virus Variants.* **Cold Spring Harbor Meeting on Retroviruses**, Cold Spring Harbor, NY [invited lecture]

3. 06/25/2016: *Germline DNA Repair Gene Mutations in Metastatic Prostate Cancer.* **2016 Prostate Cancer Foundation Coffey-Holden Academy**, Coronado, CA [invited lecture]

4. 11/30/2016: *Clinical Implications for Prostate Cancer Screening and Treatment of Men with Germline Mutations in BRCA and other DNA Repair Genes.* The 17th Annual Meeting of the **Society of Urologic Oncology**, San Antonio, TX [invited lecture]

5. 06/05/2017: *Clinical Implications of Genomic Sequencing in Prostate Cancer.* **American Society for Clinical Oncology Annual Meeting**, Chicago, IL [invited abstract discussant]

6. 10/06/2017: *Beyond the Androgen Receptor II: New Approaches to Understanding and Treating Metastatic Prostate Cancer; Report from the 2017 Coffey-Holden Prostate Cancer Academy Meeting*. 24th Annual Prostate Cancer Foundation Scientific Retreat, Washington, D.C. [invited oral presentation]

7. 10/06/2017: *Implementing Germline Genetics into Prostate Cancer Clinical Care*. **24th Annual Prostate Cancer Foundation Scientific Retreat**, Washington, D.C. [invited oral presentation]

8. 02/09/2018: *A New Era in Prostate Cancer Treatment? Understanding DNA Repair Deficiencies and the Therapeutic Rationale for PARP Inhibition.* Genitourinary Cancers Symposium CME, San Francisco, CA. [invited CME faculty]

9. 02/11/2018: *The Changing Landscape of Prostate Cancer Genetics Care and the GENTleMEN Study*, **Morris Kahn and Maccabi Research and Innovation Institute, Tel Aviv, Israel** [invited oral presentation]
10. 02/12/2018: *The Changing Landscape of Prostate Cancer Genetics Care and the GENTleMEN Study,* **Sheba Medical Center/Tel Hashomer Hospital, Tel Aviv, Israel** [invited oral presentation]

11. 03/29/2018: *Expanding Clinical and Research Horizons in Prostate Cancer Genetics.* Koch Center Seminar Series, **MD Anderson Cancer Center**, Houston, TX. [invited faculty speaker]

12. 05/20/2018: *Genetic Testing in Prostate Cancer: Understanding Clinical Implications for Early Detection, Localized disease, and CRPC.* **Annual Meeting of the American Urological Association**, San Francisco. [educational course faculty]

13. 06/01/2018: *Genomics Versus Genetics, and Implications for Prostate Cancer Care.* **American Society of Clinical Oncology Annual Meeting**, Chicago, IL [invited session chair and oral presentation]

14. 09/15/2018: *Genetics and Genomics in Prostate Cancer: Realizing the Promise of Precision Medicine and Other Very Important Benefits.* Prostate Cancer Symposium, **Barbara Ann Karmanos Cancer Institute**, Wayne State University School of Medicine, Detroit, MI [invited Keynote Lecture]

15. 05/03/2019: *Genetic Testing in Prostate Cancer: Understanding Clinical Implications for Early Detection, Localized disease, and CRPC.* **Annual Meeting of the American Urological Association**, San Francisco. [educational course faculty]

16. 05/31/2019*: The Genetic Landscape and Prognostic/Predictive Implications*. 2019 ASCO Genetics and Genomics Pre-Annual Meeting Seminar, **American Society of Clinical Oncology Annual Meeting**, Chicago, IL [invited faculty speaker]

17. 09/11/2019: *Expanding Clinical and Research Horizons in Prostate Cancer Genetics*. Oncology Grand Rounds, **University of Wisconsin/Carbone Cancer Center**, Madison, WI [invited Grand Rounds speaker**]**

18. 10/04/2019: *Germline Contribution to Metastatic Prostate Cancer.* Implementation of Genetic Testing for Inherited Prostate Cancer, **Philadelphia Prostate Cancer Consensus Conference 2019**. [invited speaker]

19. 10/26/2019: *Prostate Cancer Genetics.* Prostate Cancer Foundation and UsTOO International Prostate Cancer Support Network, **26th Prostate Cancer Foundation Annual Scientific Retreat**. Carlsbad, CA. [invited speaker]

20. 11/06/2019: *Molecular-Driven Therapy in GU Cancers.* **37th Annual CFS®: Innovative Cancer Therapy for Tomorrow**, New York, NY [invited faculty speaker]

21. 04/18/2020: *Prostate Cancer, DNA Repair Pathways and Predictive Testing for Inherited Cancers*. **9th Annual International Clinical Cancer Genetics and Genomics Conference, University of Chicago**; Chicago, IL [invited faculty speaker]

22. *(cancelled due to COVID19*) 05/20/2020: *Genetic Testing in Prostate Cancer: Understanding Clinical Implications for Early Detection, Localized disease, and CRPC.* **Annual Meeting of the American Urological Association, Washington, D.C**. [educational course faculty]

23. 10/14/2020: *Prostate Cancer Genetics: Testing, Targeted Therapy and Early Detection.* **Dana-Farber Genitourinary Oncology Seminar Series**, Boston, MA [invited faculty speaker]

24. 10/15/2020: *Genetics, Genomics, and Prostate Cancer.* USToo International, Chicago, IL [invited webinar speaker]. https://www.youtube.com/watch?v=WjkAF1xixOA&feature=youtu.be

25. 11/20/2020: *Genetic Testing in Prostate Cancer.* **Facing Our Risk of Cancer Empowered Annual Conference, Philadelphia, PA.** [invited faculty]. https://www.youtube.com/watch?v=m515URd9uYk&feature=youtu.be

26. 04/29/2021: *Integrating Genetic Testing into Clinical Practice for Advanced Prostate Cancer*. Genitourinary (GU) Medical Oncology Series: The Impact of Genomic Profiling on Patients with Prostate Cancer. LUGPA Webinar [invited faculty speaker]

27. 07/29/2021: *What is Right for Me in My Prostate Cancer Treatment – Genetics & Genomics.* **USToo International, Chicago, IL** [invited national webinar speaker]

28. 09/20/2021: *Genetic Testing in Prostate Cancer: Understanding Clinical Implications for Early Detection, Localized Disease, and CRPC.* **Annual Meeting of the American Urological Association, Washington, D.C**. [educational course faculty]

29. 09/20/2021: *Germline Genetics for Prostate Cancer Prognosis: Predicting Drug Treatment Response for Men with Advanced Prostate Cancer (Urologic Oncology Research Symposium)* **Annual Meeting of the American Urological Association, Washington, D.C**. [invited faculty speaker]

30. 09/29/2021: *What's New in Prostate Cancer Treatment*. **12th Annual FORCE Hereditary Cancer Conference, Philadelphia, PA** [invited national webinar faculty]

31. 04/29/2022: *How to take care of muscle strength for prostate cancer patients.* **Advanced Prostate Cancer Consensus Conference 2022, Lugano, Switzerland** [invited faculty speaker and session chair]

32. 05/15/2022: *Genetic Testing in Prostate Cancer: Understanding Clinical Implications for Early Detection, Localized Disease, and CRPC.* **Annual Meeting of the American Urological Association, New Orleans, LA**. [educational course faculty]

33. 06/06/2022: *AR and PARP: Partners in Crime.* **American Society of Clinical Oncology 2022 Annual Meeting, Chicago, IL** [invited oral poster discussant]

34. 10/13/2022: *What's New in Prostate Cancer Treatment*. **13th Annual FORCE Hereditary Cancer Conference, Philadelphia, PA** [invited national webinar faculty]

35. *(anticipated)* 01/28/2023: *Testing for Hereditary Cancer Predisposition.* University of California at San Diego Prostate Cancer Patient Summit, San Diego, CA [invited speaker]

36. *(anticipated)* 05/05/2023: *Bringing Prostate Cancer Risk Assessment to the Community: A GENTleMEN's PROMISE.* City of Hope/University of Chicago **11th Annual Clinical Cancer Genomics Conference**, Los Angeles, CA [invited speaker]

37. *(anticipated)* 05/15/2023: *Genetic Testing in Prostate Cancer: Understanding Clinical Implications for Early Detection, Localized Disease, and CRPC.* **Annual Meeting of the American Urological Association, New Orleans, LA**. [educational course faculty]

38. *(anticipated)* 06/05/2023: *Genetics and Genomics: Beyond DNA Repair.* **American Society for Clinical Oncology 2023 Annual Meeting, Chicago, IL**, [invited session chair and speaker]

b. Regional Invited Lectures

1. 07/15/2012: *Circulating microRNA Biomarkers in Prostate Cancer*. Oral presentation for Department of Defense/Prostate Cancer Clinical Trials Consortium. Teleconferenced nationally from Memorial Sloan Kettering Cancer Center, New York, NY

2. 11/20/2013: *A Phase I/II Trial of Concurrent Chemohormonal therapy using Enzalutamide and Cabazitaxel in Patients with Metastatic Castration Resistant Prostate Cancer.* Oral presentation, teleconferenced nationally from Memorial Sloan Kettering Cancer Center, New York, NY

3. 04/12/2014: *Circulating Biomarkers in Advanced Disease***.** Institute for Prostate Cancer Research 2014 Symposium, Fred Hutchinson Cancer Research Center, Seattle, WA.

4. 05/01/2014**:** *Comparison of plasma microRNAs with CTCs and PSA in patients treated on SWOG S0925.* Oral presentation at 2014 SWOG Genitourinary Working Group Meeting, San Francisco, CA

5. 06/20/2014: *Recent Developments and Clinical Trials in Prostate Cancer.* Oral presentation for the Seattle Cancer Care Alliance/National Comprehensive Cancer Network "Breakthroughs in Solid Tumor Oncology" Symposium; June 20, 2014, Seattle, WA

6. 10/31/2014: *Comparison of plasma microRNAs with CTCs and PSA in patients treated on SWOG S0925.* Prostate Cancer SPORE Seminar, Fred Hutchinson Cancer Research Center, teleconferenced to Oregon Health Sciences and University of British Columbia

7. 06/29/2016: *Emerging Therapies in Cancer: Cancer Genetics.* Seattle Cancer Care Alliance CME lecture for Skagit Valley Hospital, Mount Vernon, WA

8. 10/27/2016: *Prostate Cancer Foundation Women's Networking Forum*. Junior Investigator Panelist at the 2016 Prostate Cancer Foundation Retreat, Carlsbad, CA

9. 04/13/2017: *Metastatic Prostate Cancer*. Cases From Kampala, hosted by Uganda Cancer Institute/Hutchinson Cancer Center Alliance; WebEx between Seattle, WA, and Kampala, Uganda

10. 09/23/2017**:** *The Genetics of Inherited Prostate Cancer Risk: Why what has always mattered matters even more in 2017*. 17th Annual Pacific NW Prostate Cancer Conference, Seattle, WA

11. 02/01/2018: *Genetic Testing for Men with Metastatic Prostate Cancer: Changing Landscape and the GENTleMEN Study.* PPCR SPORE Seminar Series, Fred Hutch Cancer Research Center, Seattle, WA

12. 03/08/2018: *Precision Medicine for Older Adults: Delivering on a Promise*. Plein Research Symposium in Geriatric Pharmacy, Center for Urban Horticulture, Univ of Washington, Seattle, WA

13. 06/23/2018: *Prostate Cancer Pathways for Patients and Caregivers: Updates in Prostate Cancer Genetics*. UsTOO International Prostate Cancer Support Network Patient Symposium and Webcast, Evergreen Hospital, Kirkland, WA

14. 07/17/2018*: Molecular Predictors of Prostate Cancer Progression and Mortality*. PNW SPORE Symposium, Fred Hutch Cancer Research Center, Seattle, WA, , teleconferenced to Oregon Health Sciences and University of British Columbia

15. 10/12/2018: *Prostate Cancer.* Transitions in Oncology Care: Pearls for the Primary Care Provider Conference, Talaris Conference Center, Seattle, WA.

16. 10/15/2018: *Expanding Clinical and Research Horizons in Prostate Cancer Genetics*. Fred Hutch Clinical Research/University of Washington Medical Oncology/Seattle Cancer Care Alliance, Clinical Research Division Seminar Series, Seattle, WA

17. 05/11/2019: *Genetics: The GENTleMEN study and extending potential benefit to families.* Prostate Cancer Symposium, hosted by the Institute for Prostate Cancer Research; Fred Hutch Cancer Research Center, Seattle, WA

18. 07/22/2020: *Prostate Cancer Genetics.* Medscape CME Webinar; Seattle Cancer Care Alliance, Seattle WA

19. 09/24/2020: *Prostate Cancer Genetics in 2020: Testing, Targeted Therapy and Early Detection.* PPCR SPORE Seminar Series, Fred Hutch Cancer Research Center, Seattle, WA, teleconferenced to Oregon Health Sciences and University of British Columbia

20. 03/06/2021: *Updates in Genetics for Bladder and Urinary Tract Cancer.* Updates in Bladder and Urinary Tract Cancers; Seattle Cancer Care Alliance, Seattle WA

21. 7/30/2022: *Risk-Based Screening and Hereditary Prostate Cancer*. Breakthroughs in Prostate Cancer Research. Institute for Prostate Cancer Research Symposium; Seattle, WA

22. 10/15/2022: *What You Should Know About the Growing Importance of Genetic Testing in Prostate Cancer*. 22nd Annual Pacific NW Prostate Cancer Conference; Seattle, WA [invited webinar faculty]

c. Local Invited Lectures

1. 09/25/2014: *Prostate Cancer: New Treatments and Ongoing Research.* Fred Hutchinson Cancer Research Center Diversity/Outreach Program to local African American Community, NW African American Museum, Seattle, WA.

2. 11/12/2014: *The Surprising Ways in Which Patients Shape our Lives.* Schwarz Center Rounds, hosted by The Schwarz Center for Compassionate Healthcare; Seattle Cancer Care Alliance, Seattle, WA

3. 04/11/2015: *Lessons from Breast Cancer: How Genes May Affect Risk, Treatment and Outcomes in Prostate Cancer.* Prostate Cancer Symposium, hosted by the Institute for Prostate Cancer Research; Fred Hutchinson Cancer Research Center, Seattle, WA

4. 05/07/2015*: Prostate Cancer: Progress Made and Research in Progress.* Research Matters Series, Seattle Cancer Care Alliance, Seattle, WA

5. 03/24/2016: *Leveraging DNA Repair Defects for Treatment of Prostate Cancer.* PPCR SPORE Seminar Series, Fred Hutchinson Cancer Research Center, Seattle, WA

6. 10/11/2016: *New Discoveries in Prostate Cancer Genetics (or: Why Breast Cancer Genes Are Not Just for Women)*". Fred Hutch Clinical Research/University of Washington Medical Oncology/Seattle Cancer Care Alliance Grand Round, Seattle, WA

7. 11/17/2016: *Prostate Cancer Genetics: Leveraging Family Traits for Early Detection***.** Fred Hutchinson Cancer Research Center Innovators Network. Seattle, WA

8. 12/23/2016: *Testicular Cancer/Germ Cell Tumors*. UW/Fred Hutch Hematology/Oncology Fellows Lecture Series, Seattle, WA.

9. 03/18/2017: *Inherited Risk and Prostate Cancer Behavior.* Prostate Cancer Symposium, Institute for Prostate Cancer Research; Fred Hutchinson Cancer Research Center, Seattle, WA

10. 05/24/2017: *Prostate Cancer Genetics.* UsTOO Greater Seattle Area Prostate Cancer Patient Support Group; Greenwood Community Center, Seattle, WA.

11. 10/26/2017: *Clinical Implementation of Quality of Life Measurement in Prostate Cancer Care.* PPCR SPORE Seminar Series, Fred Hutchinson Cancer Research Center, Seattle, WA

12. 11/06/2017: *Genetics and Genomics.* CCSG Prostate Program Cancer Retreat, Fred Hutchinson Cancer Research Center, Seattle, WA

13. 01/19/2018: *Testicular Cancer/Germ Cell Tumors*. UW/Fred Hutch Hematology/Oncology Fellows Lecture Series, Seattle, WA.

14. 01/26/2018: *Expanding Clinical and Research Horizons in Prostate Cancer Genetics.* **UW Medical Genetics Division Grand Rounds**, Seattle, WA

23. 04/28/2018: *Inherited Risk and GENTleMEN.* Prostate Cancer Symposium, hosted by the Institute for Prostate Cancer Research; Fred Hutch Cancer Research Center, Seattle, WA

24. 05/04/2018: *Genetic Testing for Men with Metastatic Prostate Cancer: GENTleMEN.* Seattle Cancer Care Alliance Network Summit, Fred Hutch Cancer Research Center, Seattle, WA

25. 05/07/2018: *Prostate Cancer: Screening, Treatment and Genetics.* UW Internal Medicine Residents Report, University of Washington Medical Center, Seattle, WA

26. 05/23/2018: *Prostate Cancer Genetics and the GENTleMEN Study*. CCSG Breast and Ovary Cancer Research Program Retreat, Fred Hutch Cancer Research Center, Seattle, WA

27. 08/09/2018: *Prostate Cancer Genetics and the GENTleMEN Study*. Overbaugh Lab 30th Year Symposium Retreat, Islandwood, Bainbridge Island, WA

28. 10/05/2018: *Testicular Cancer/Germ Cell Tumors*. UW/Fred Hutch Hematology/Oncology Fellows Lecture Series, Seattle, WA.

29. 09/06/2019: *Germline and Somatic DNA repair mutations in Prostate Cancer.* Genitourinary Medical Oncology Research Team Staff Education Series; Fred Hutch Cancer Research Center, Seattle, WA

30. 09/06/2019: *Updates in Prostate Cancer Genetics.* Seattle Cancer Care Alliance Community Site Dinner Clinical Research Partnership Series; Seattle, WA

31. 01/09/2020: *From Cat Viruses to Men's Prostates: An Ongoing Research Journey.* UW Medical Scientist Training Program Monthly Research Meeting; Seattle, WA.

32. 01/24/2020: *Mutational Testing for Solid Tumors.* UW/Fred Hutch Hematology and Oncology Fellowship Solid Tumor Conference; Seattle, WA.

33. 01/29/2020: *Prostate Cancer: Screening, Side Effects and Survivorship.* Genitourinary Medical Oncology Research Team Staff Education Series; Fred Hutch Cancer Research Center, Seattle, WA

34. 05/27/2020: *Prostate Cancer Genetics through a Medical Oncologist's Lens.* **University of Washington, Radiation Oncology Grand Rounds**, Seattle, WA. [invited Grand Rounds]

35. 07/15/2020: *Olaparib for Metastatic Castration Resistant Prostate Cancer.* Clinical Research Division Journal Watch; Fred Hutch Cancer Research Center, Seattle, WA

36. 02/22/2021: *Prostate Cancer Genetics and Risk.* Seattle Cancer Care Alliance Board Enrichment Series; Seattle Cancer Care Alliance, Seattle WA

37. 06/06/2021: *Molecular Subtypes and Prostate Cancer Treatments.* Prostate Cancer Symposium, hosted by Institute for Prostate Cancer Research; Fred Hutch Cancer Research Center, Seattle, WA

38. 08/25/2021: *Role of Genes in Prostate Cancer and the PROMISE Study.* USToo Support Group Meeting, Seattle, WA

39. 7/21/2022: *Genetics and Genomics of Prostate Cancer*. Genitourinary Medical Oncology Research Staff Education Series; Seattle, WA

CURRICULUM VITAE

EVAN YA-WEN YU, MD
825 Eastlake Ave E, G4-830
Seattle, WA 98109

PERSONAL DATA

Place of birth:
Citizenship:
Date of Birth:
Languages: English, Mandarin Chinese

EDUCATION

B.S. (Zoology) University of Washington, Seattle, WA	1989-1994
M.D. University of Washington, School of Medicine, Seattle, WA	1994-1998

POSTGRADUATE TRAINING

Clinical Fellow in Medicine, Harvard Medical School, Boston, MA	1998-2004
Intern in Medicine, Brigham and Women's Hospital, Boston, MA	1998-1999
Junior Assistant Resident, Brigham and Women's Hospital, Boston, MA	1999-2000
Senior Assistant Resident, Brigham and Women's Hospital, Boston, MA	2000-2001
Fellow in Hematology-Oncology, Dana-Farber Cancer Institute, Boston, MA	2001-2004
Clinical Fellow in Medicine, Brigham and Women's Hospital, Boston, MA	2001-2004
Post-doctoral Basic Science Research Fellow, Dana-Farber Cancer Institute William C. Hahn, M.D., Ph.D., Boston, MA	2002-2004
AACR/ASCO Methods in Clinical Cancer Research Workshop	2006

FACULTY POSITIONS HELD

Assistant Professor, Department of Medicine, School of Medicine University of Washington, Seattle, WA	2004-2010
Assistant Member, Clinical Research Division Fred Hutchinson Cancer Research Center, Seattle, WA	2004-2010
Assistant Fellowship Director Medical Oncology and Hematology Fellowship Program University of Washington / Fred Hutchinson Cancer Research Center, Seattle, WA	2006-2017
Associate Professor, Department of Medicine, School of Medicine University of Washington, Seattle, WA	2010-2016
Associate Member, Clinical Research Division Fred Hutchinson Cancer Research Center, Seattle, WA	2010-2016
Clinical Trials Core Director Genitourinary Medical Oncology Research Group University of Washington / Fred Hutchinson Cancer Research Center, Seattle, WA	2012-2022

Full Professor, Department of Medicine, School of Medicine
University of Washington, Seattle, WA 2016-present

Full Member, Clinical Research Division
Fred Hutchinson Cancer Research Center, Seattle, WA 2016-present

Clinical Research Director
Genitourinary Oncology Research Group
University of Washington / Fred Hutchinson Cancer Research Center, Seattle, WA 2017-2022

Medical Director
Clinical Research Support
Fred Hutchinson Cancer Consortium, Seattle, WA 2018-present

Section Head
Medical Oncology, Division of Cancer Medicine
Fred Hutchinson Cancer Center, Seattle, WA 2022-present

HOSPITAL POSITIONS HELD

Member, Medical Staff, Pembroke Psychiatric Hospital, Pembroke, MA 2000-2001
Member, New England Sinai Rehabilitation Hospital, Stoughton, MA 2000-2001
Member, Medical Staff, Anna Jacques Hospital, Newburyport, MA 2000-2002
Member, Medical Staff, South Shore Hospital, Weymouth, MA 2001-2002
Member, Medical Staff, Emerson Hospital, Concord, MA 2001-2004
Member, Medical Staff, Jordan Hospital, Plymouth, MA 2000, 2004
Member, Medical Staff, Faulkner Hospital, Boston, MA 2004
Member, Medical Staff, Brigham and Women's Hospital, Boston, MA 2004
Member, Medical Staff, University of Washington Medical Center, Seattle, WA 2004-present

HONORS

Alpha Omega Alpha, School of Medicine, University of Washington 1997
Graduation with Honors, School of Medicine, University of Washington 1998
Chief Resident, Faulkner Hospital (Subsidiary of Brigham and Women's Hospital) 2001
Seattle Magazine's "Top Doctor" 2010, 2018, 2022
Who's Who in Medicine and Healthcare 2011-2012
Seattle Met Magazine's "Top Doctor" 2011
U.S. News and World Report "Top Doctor" 2011-present
Castle Connolly America's Top Doctors 2011-present
Invited Faculty for "Fellows, Residents and Junior Faculty Networking Luncheon"
Genitourinary Cancers Symposium 2012, 2013
Asian Journal of Andrology "Excellent Editorial Board Member Award" 2016
Albert Nelson Marquis Lifetime Achievement Award 2017
Who's Who in Academia 2017-present
"Triple Threat Award," Fred Hutchinson Cancer Research Center Assistant Fellowship Director 2018
"Best of the Best," Top 1% America's Most Honored Professionals 2018-present
William J. Bremner Endowed Department of Medicine Mentorship Award Nominee 2018
Outstanding Research Mentor Award, E17 University of Washington School of Medicine 2019
Philip Saccoccia Montana WWAMI Translational Medicine Speaker 2021
America's Most Honored Doctors – Top 5% 2022 2022

BOARD CERTIFICATION

American Board of Internal Medicine	2001-2011
Medical Oncology	2003-present (recertified in 2013)

MEDICAL LICENSE

State of Massachusetts	2000-2005
State of Washington (MD00044089)	2004-present
State of Montana (MED-PHYS-LIC-102493)	2021-present

NPI #1043390016

Diversity, Equity and Inclusion Activities:

Diverse Enrollment Institutional Review Board Subcommittee Fred Hutchinson Cancer Research Consortium	2021-present
Cancer Center Director's Task Force for DEI in Clinical Investigations Fred Hutchinson Cancer Research Consortium	2021-present
Asian American Cancer Disparities Webinar American Cancer Society	2022

PROFESSIONAL ORGANIZATIONS

American Association of Cancer Research
American Medical Association
American Radium Society
American Society of Clinical Oncology
American Society of Internal Medicine
American Urological Association
Association of American Cancer Institutes
European Society of Medical Oncology
Hoosier Cancer Research Network
Massachusetts Medical Society
Society for Immunotherapy of Cancer
Society of Urologic Oncology
Southwest Oncology Group (SWOG)
Washington State Medical Oncology Society

TEACHING RESPONSIBILITIES

Tutor, Basic Sciences, Microbiology and Biochemistry, School of Medicine, University of Washington	1997-1998
Adjunct Instructor, Health Sciences, Massachusetts College of Pharmacy	1999-2000
Adjunct Instructor, Health Sciences, Massachusetts School of Health Sciences	1999-2000
Preceptor, Patient-Doctor II Course, Harvard Medical School	2004
Teaching of Fellows, Residents, and Medical Students, University of Washington	2004-present
Research Mentor, American Cancer Society Medical Student Research Program, University of Washington (Student - Brian Rezvani)	2007
Preceptor, University of Washington School of Medicine (Students Andrew Stergachis, Michael Zhang, Gabriel Loeb, Erica Nees, and Qian Zhang)	2008-2011
Research Mentor (Students), University of Washington	
Brian B. Rezvani – Now thoracic surgeon	2007
Kevin F. Kuo – Now internal medicine faculty at Stanford University	2009-2013

Jason Flamiatos – Now Urologist 2011-2013
Daniel Lim – Current internal medicine resident at University of Washington 2017-present
Alex Carlson – Now internal medicine resident at University of Wisconsin 2018-2020
Olivia Do – Current pediatrics resident at University of Washington 2019-2021
Lorin Ferris – Current pediatrics resident at Inova L.J. Murphy Children's Hospital 2019-2021

Research Mentor (Fellows), Fred Hutchinson Cancer Research Center Oncology Fellowship

Junfeng Wang – Assistant Professor at University of Utah and Huntsman Cancer Institute (Division of Oncology, Department of Medicine) 2012
Swaminathan Murugappan – Now Executive Medical Director at Kite 2012
Heather H. Cheng – Now Associate Professor at University of Washington 2012-present
Jorge D. Ramos –Assistant Professor at University of Washington, now Medical Director at Seattle Genetics 2013-2017
Risa Wong – Now Assistant Professor at University of Pittsburgh 2019-2021
Rafee Talukder – Current hematology/oncology fellow 2021-present

EDITORIAL RESPONSIBILITIES

Senior/Associate Editor

Clinical Genitourinary Cancer 2016-2018
UroToday (Clinical Trials Portal) 2016-present
Clinical Cancer Research 2017-present

Editorial Board

Clinical Genitourinary Cancer 2010-2018
Journal of Cancer Therapeutics and Research 2011-2017
Asian Journal of Andrology 2015-2018
Everyday Oncology 2016-2017

"Ad hoc" Reviewer

Annals of Oncology, Asian Journal of Urology, Bladder Cancer Journal, British Journal of Cancer, BMC Cancer, British Journal of Urology International, Cancer, Cancer Control Journal, Cancer Discovery, Clinical Cancer Research, Clinical Interventions in Aging, Clinical Medicine Insights: Oncology, Drugs, European Journal of Cancer, European Urology, Expert Opinions on Investigational Drugs, Expert Review of Anticancer Therapy, Investigational New Drugs, Journal of American Medical Association, Journal of Clinical Endocrinology and Metabolism, Journal of Clinical Investigation, Journal of Clinical Oncology, JCO Clinical Cancer Informatics, Journal of ImmunoTherapy of Cancer, Journal of the National Cancer Institute, Journal of the National Comprehensive Cancer Network, Journal of Nuclear Medicine, Journal of Oncotargets and Therapy, Journal of Urology, Lancet Oncology, New England Journal of Medicine, The Oncologist, Oncotarget, PLOS ONE, Proceedings of the National Academy of Sciences, The Prostate, Prostate Cancer and Prostatic Diseases, Up-to-Date: Genitourinary Oncology, Urologic Oncology, Urology

Grant and Funding Organization Reviews

Cancer Research United Kingdom, Department of Defense, National Cancer Institute, Prostate Cancer Charity, Prostate Cancer Foundation Challenge and Young Investigator Awards, PNW SPORE Pilot Projects, Solid Tumor Translational Research (STTR) Grant Program, V Foundation

NATIONAL RESPONSIBILITIES

Reviewer, Department of Defense 2005
Prostate Cancer Translational Grant Study Section
Steering Committee Member, Dasatinib Phase 3 Registration Study 2009-2013

Imaging Committee, Prostate Cancer Working Group 2009-2012
Co-Chair and Faculty, 2010 American Society of Clinical Oncology 2010
Genitourinary Cancer (Prostate) Oral Abstract Session
Co-Chair, Quantitative Imaging Network (QIN) Outreach Working Group 2010
Genitourinary Committee Member, SWOG 2010-present
Co-Chair and Faculty, 2011 American Society of Clinical Oncology 2011
Genitourinary Cancer (Non-Prostate) Oral Abstract Session
Advanced Prostate Cancer Chair (covering), SWOG Fall 2011 Group Meeting 2011
Genitourinary Committee
SPORE Representative, National Cancer Institute 2012-2014
Genitourinary Cancers Steering Committee
Steering Committee Member, PREDICT Biomarker Committee 2013-2016
Special Clinical Expert, National Cancer Institute (Served 1 year of 2nd 3-year term) 2014-2018
Genitourinary Cancers Steering Committee
Advisory Member, Society of Urology Oncology (Clinical Trials Consortium, Inc.) 2015-present
Board of Directors and the Prostate Organ Site Committee
Test Question Writer, American Society of Clinical Oncology and National Board of 2017-2019
Medical Examiners
ASCO University Courses, ASCO-SEP Mock Exam, In-Training Exam
Member, American Society of Oncology Annual Meeting Education Committee 2017-2020
Genitourinary (Nonprostate) Cancer
Member, Bone Metastasis Expert Panel 2017-2019
American Radium Society
GU Prostate Cancer Committee Member, SWOG 2017-present
Co-Chair (Medical Oncology), National Cancer Institute (3-year term renewed) 2018-present
Prostate Cancer Task Force
Imaging Committee Member, SWOG 2018-present
Member, Education Committee 2019-present
Association of American Cancer Institutes
Member, Board of Governors, SWOG 2020-present
Member, AACR Annual Meeting Clinical Trials Committee 2020-2022
American Association for Cancer Research
Test Question Writer, American Society of Clinical Oncology Question Writing 2021-present
Group for ASCO Self-Assessment Programs
Reviewer, National Cancer Institute 2021
Cancer Clinical Investigator Team Leadership Award (CCITLA) Grant Reviewer
Co-Chair, American Society of Clinical Oncology 2021-present
Germline and Somatic Genomic Testing for Advanced and Metastatic Prostate Cancer
Reviewer, National Cancer Institute Intramural Research Program 2021
Molecular Imaging Branch
Member, Hoosier Cancer Research Network 2021-present
Genitourinary Clincal Trial Working Group
Member, AACR Continuing Medical Education Committee 2022-present
American Association for Cancer Research
Member, Imaging Committee 2022- present
Prostate Cancer Working Group 4

LOCAL RESPONSIBILITIES

4th Floor Solutions Committee, 2004–2006
Seattle Cancer Care Alliance

Genitourinary Practice Committee 2004–2005
University of Washington Department of Medicine
Recruitment and Community Outreach Core 2004–2005
University of Washington Translational Grant Committee
Multicultural Affairs Advisory Board 2006–2007
University of Washington Department of Medicine
Translational Research Task Force 2006–2008
University of Washington Translational Grant Committee
Accreditation Council for Graduate Medical Education 2006–2017
University of Washington Medicine Residency Program
Oncology and Hematology Fellowship Program Admissions Committee 2006–present
University of Washington / Fred Hutchinson Cancer Research Center
Prostate Cancer Task Force 2007–2008
Washington Comprehensive Cancer Control Partnership
Imaging Working Group 2007–2008
Prostate Specialized Programs of Research Excellence (SPORE)
Quality Improvement/Safety Steering Committee 2007–2010
Seattle Cancer Care Alliance
Medical Student Research Training Program Committee 2008-2016
University of Washington School of Medicine
Medical Student Admissions Committee 1995-1998
University of Washington School of Medicine 2009-2016
Institute for Prostate Cancer Research Committee 2009-present
University of Washington
Grant Reviewer 2010
INBRE-WSU Spokane Institute for Translational Health Sciences
Internal Medicine Residency Education Coordinator (Oncology) 2010-2017
University of Washington
Core Faculty Designation, Internal Medicine Residency 2010-present
University of Washington
Clinical Core Director 2012-present
Pacific Northwest Prostate Cancer SPORE
Reviewer for the University of Washington 2013
American Cancer Society Summer Fellowship in Clinical Cancer Research
New Faculty Search Committee Member 2013-2015
University of Washington Pediatric Oncology and Seattle Children's Hospital
Prostate Cancer Clinical Pathways 2013-2017
Seattle Cancer Care Alliance
Scientific Review Committee, Sub-Committee B Member 2014
University of Washington / Fred Hutchinson Cancer Research Center Consortium
Scientific Review Committee, Sub-Committee B Co-Chair 2015-2017
University of Washington / Fred Hutchinson Cancer Research Center Consortium
New Radiochemistry Faculty Search Committee Member 2015-2018
University of Washington Department of Radiology
New Faculty Search Committee Member 2016-2017
University of Washington Genitourinary Oncology
Genitourinary Oncology Leadership Committee 2017-present
University of Washington / Fred Hutchinson Cancer Research Center Consortium
Clinical Trials Process Improvement Oversight Committee 2017-present
Seattle Cancer Care Alliance

External Performance Site Assessment Committee 2018
Fred Hutchinson Cancer Consortium
Site Initiation Visit Escalation Policy Committee 2017-2018
Seattle Cancer Care Alliance
New Faculty Search Committee, Director of Nuclear Medicine 2018-2019
Seattle Cancer Care Alliance
Research Ethics Committee 2018-present
Fred Hutchinson Board of Trustees
Institutional Review Board Chair Liason Committee 2018-present
Fred Hutchinson Cancer Research Consortium
Compliance Sub-Committee, Clinical Research Services 2018-present
Fred Hutchinson Cancer Research Consortium
Clinical Trial Oversight Committee, Clinical Research Services 2018-present
Fred Hutchinson Cancer Research Consortium
Institutional Sponsored IND Oversight Committee, Clinical Research Services 2018-present
Fred Hutchinson Cancer Research Consortium
NCI National Cancer Trials Network Leadership Committee 2020-present
Fred Hutchinson Cancer Research Consortium
Adult Oncology Strategic Plan: Research Advisory Group 2021-present
Seattle Cancer Care Alliance/University of Washington Medicine/Fred Hutchinson Cancer Research Center
New Faculty Search Committee, Director of Nuclear Medicine Theranostics 2021-present
Seattle Cancer Care Alliance
Co-Chair, Faculty Advisory Committee, Clinical Trials Joint Steering Committee 2022-present
University of Washington and Fred Hutchinson Cancer Center

PEER REVIEW FUNDING

1. Prostate Cancer Research Program Clinical Consortium Award.
   W81XWH-16-PCRP-CCRSA (Cheng)
   Grant amount:
   Source: Department of Defense
   Role: Co-site principal investigator (5% effort)
   Dates: 01/01/07 - 09/29/27 (4 successful competitive renewals)

2. Pacific Northwest Prostate Cancer SPORE – Core D (Clinical)
   P50 CA097186 (Nelson/Core D Yu and Gore)
   Grant amount: (this funding cycle)
   Source: Pacific Northwest Prostate Cancer SPORE
   Role: Clinical Core Leader for clinical trials and biospecimen acquisition
   Dates: 9/17/13 – 08/31/23 (2 successful competitive renewals)

3. Cancer Consortium Support Grant
   P30 CA015704 (Gilliland) / Clinical Research Support (Yu)
   Grant amount:
   Role: Medical Director, Clinical Research Support Office
   Dates: 01/01/97 – 12/31/24

4. Lead Academic Participating Site (LAPS) Grant
   UG1 CA233328 (Yu)
   Grant Amount:
   Source: NIH/NCI
   Role: Site co-Principal Investigator
   Dates: 03/06/19 - 02/28/25

PEER REVIEW FUNDING: COMPLETED

1. Pilot Project - Positron Emission Tomography Imaging of Bone in Patients with Metastatic Prostate Cancer - A Pilot Study Evaluating Treatment Response.
   5 P30 CA015704 (Hartwell) / Pilot (Yu)
   Grant amount:
   Source: NIH/NCI Cancer Center Support Grant
   Role: Concept development and overall principal investigator
   Dates: 10/01/05 – 12/31/07

2. Pilot Project - Positron Emission Tomography Imaging of Bone in Patients with Metastatic Prostate Cancer.
   P50 CA97186 (Lange) / Pilot (Yu)
   Grant amount:
   Source: Pacific Northwest Prostate Cancer SPORE
   Role: Concept development and overall principal investigator
   Dates: 01/01/07 – 12/31/07

3. A randomized phase II study of OGX-011 in combination with docetaxel and prednisone or docetaxel and prednisone alone in patients with metastatic hormone-refractory prostate cancer.
   Grant amount:
   Source: National Cancer Institute of Canada (Cooperative Group Trial)
   Role: Site Principal Investigator
   Dates: 11/01/05 – 09/30/09

4. Phase 2 randomized trial of gemcitabine and cisplatin with or without Cetuximab in patients with urothelial carcinoma.
   Grant amount:
   Source: National Comprehensive Cancer Network (Cooperative Group Trial)
   Role: Site principal investigator
   Dates: 01/15/09 - 03/04/11

5. Phase 2, multicenter evaluation of ^{18}F-fluoride PET as a pharmacodynamic biomarker for Dasatinib, a SRC kinase inhibitor, in men with castration-resistant prostate cancer and bone metastases (ACRIN 6687).
   Grant amount:
   Source: American College of Radiology Imaging Network (ACRIN) (Cooperative Group Trial)
   Role: Concept development, multicenter study chair, and overall principal investigator (20% effort)
   Dates: 07/01/09 – 06/30/12

6. Genitourinary Oncology Clinical Trials Core.

Infrastructure Support Proposal (PI: Yu)
Grant amount:
Source: Institute of Prostate Cancer Research
Role: Core Director
Dates: 11/19/12 – 11/18/13

7. A randomized phase 2 study of combined androgen deprivation versus combined androgen deprivation with Cixutumumab (IMC-A12) for patients with new hormone-sensitive metastatic prostate cancer (SWOG 0925).
Grant amount:
Source: Southwest Oncology Group (SWOG) (Cooperative Group Trial) and Imclone Pharmaceuticals
Role: Concept development, multicenter study chair, and overall principal investigator
Dates: 06/01/11 – 05/31/14

8. Advanced PET/CT imaging for improving clinical trials.
1U01 CA148131 (Kinahan)
Grant amount:
Source: National Institute of Health
Role: Leader of prostate cancer imaging trials (5% effort)
Dates: 04/16/10 – 04/15/15

9. Biomarkers of response to treatment with XL184.
Creativity Award (Co-PIs: Knudsen, Yu)
Grant amount:
Source: Prostate Cancer Foundation
Role: Concept development and leader of PET imaging effort
Dates: 05/23/12 – 08/22/16 (no cost extension)

10. A Phase II Study of MAOA Inhibitor Plus Docetaxel in Patients Currently Receiving and Progressing on Docetaxel Therapy.
Grant amount:
Source: Wayne D. Kuni and Joan E. Kuni Foundation (subcontract award from Oregon Health Sciences University)
Role: Site principal investigator
Dates: 12/01/12 – 05/31/17

11. A phase 2 study of recombinant glycosylated human interleukin-7 (CYT107) after completion of standard FDA approved therapy with sipuleucel-T for patients with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer.
Grant amount:
Source: Cancer Immunotherapy Trials Network
Role: Site principal investigator for lead site
Dates: 02/04/15 – 02/03/18

12. A pilot study of TIL therapy generation for urothelial bladder cancer.
Bezos family Immunotherapy Pilot Award (Yu)
Grant amount:
Source: Bezos family Immunotherapy Initiative

Role: Concept development and principal investigator
Dates: 07/01/15 – 06/30/18 (no cost extension)

13. INTense Exercise foR surVivAL among men with Metastatic Castrate-Resistant Prostate Cancer (INTERVAL – MCRPC): A multicenter, randomized, controlled, phase III study
Grant amount:
Source: Movember GAP4
Role: Site principal investigator
Dates: 10/05/16 – 10/04/21

PHARMACEUTICAL FUNDING: INVESTIGATOR INITIATED

1. Biologic tissue effect of sipuleucel-T on metastatic castration-resistant prostate cancer.
Grant amount:
Source: Dendreon
Role: Concept development and overall principal investigator
Dates: 01/27/15 – 04/14/23

2. A randomized phase II study of atezolizumab plus recombinant human IL-7 (CYT107) in patients with locally advanced or metastatic urothelial carcinoma.
Grant amount:
Source: Genentech, Inc. and NCI Cancer Immunotherapy Trials Network
Role: Concept development and overall national principal investigator
Dates: 06/28/19 – 09/30/23

3. The impact of DNA repair pathway alterations identified by circulating tumor DNA on sensitivity to Radium-223 in bone metastatic castration-resistant prostate cancer.
Grant amount:
Source: Bayer HealthCare Pharmaceuticals, Inc.
Role: Concept development and overall national principal
Dates: investigator 01/09/20 – 09/08/24

4. Fluciclovine (FACBC) PET/CT site-directed therapy of oligometastatic prostate cancer (FLU-BLAST-PC trial)
Grant amount:
Source: Blue Earth
Role: Concept development and overall principal investigator
Dates: 02/07/20 – 02/06/24

5. A randomized phase II study of atezolizumab plus recombinant human IL-7 (CYT107) in patients with locally advanced or metastatic urothelial carcinoma.
Grant amount: (supplemental funding agreement)
Source: Revimmune, Inc. and NCI Cancer Immunotherapy Trials Network
Role: Concept development and overall national principal investigator
Dates: 03/31/20 – 09/30/23

PHARMACEUTICAL FUNDING: INVESTIGATOR INITIATED: COMPLETED

1. A phase II study of BAY 43-9006 (Sorafenib) prior to prostatectomy in patients with high-risk localized prostate cancerGrant
amount:

Source: Bayer Pharmaceuticals, Corp.
Role: Concept development and overall principal investigator
Dates: 07/01/06 – 06/31/11

2. A randomized phase II study of docetaxel + / - ZD6474 (Zactima) in metastatic transitional cell carcinoma.
Grant amount:
Source: Astrazeneca Pharmaceuticals, LP (subcontract award from Dana-Farber Cancer Institute)
Role: Site principal investigator
Dates: 05/31/07 – 03/14/12

3. A phase II trial of genomic guided therapy with dasatinib or nilutamide in metastatic castration-resistant prostate cancer.
Grant amount:
Source: Bristol-Myers Squibb (subcontract award from Duke University)
Role: Site principal investigator with input into concept development
Dates: 05/12/09 – 12/31/12

4. Phase 2, multicenter evaluation of 18F-fluoride PET as a pharmacodynamic biomarker for Dasatinib, a SRC kinase inhibitor, in men with castration-resistant prostate cancer and bone metastases.
Grant amount:
Source: Bristol Myers Squibb Co.
Role: Concept development, multicenter study chair, and overall principal investigator
Dates: 06/01/10 – 06/30/13

5. A randomized phase II study of OGX-427 (a second-generation antisense oligonucleotide to Heat Shock Protein-27) in patients with castration resistant prostate cancer who have not previously received chemotherapy for metastatic disease.
Grant amount:
Source: OncoGeneX Techologies, Inc.
Role: Site principal investigator
Dates: 11/08/11 – 08/25/15

6. A Phase II Study of BKM120 in Men with Metastatic Castration-Resistant Prostate Cancer.
Grant amount:
Source: Novartis (subcontract award from Duke University)
Role: Site principal investigator
Dates: 07/12/13 – 09/29/15

7. Retrospective analysis of clinical benefit from radium-223 in castrate resistant prostate cancer
Grant amount:
Source: Bayer via University of Michigan
Role: Senior and site principal investigator
Dates: 05/08/15 – 05/17/17

8. PET/CT for assessment of systemic treatment response and direction of metastatic biopsy for molecular characterization of metastatic castration resistant prostate cancer

Grant amount:
Source: Bayer
Role: Concept development and overall principal investigator
Dates: 11/03/15 – 04/30/18

9. A phase 2 study of recombinant glycosylated human interleukin-7 (CYT107) after completion of standard FDA approved therapy with sipuleucel-T for patients with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer.
Grant amount:
Sources: Dendreon
Role: Site principal investigator for lead site
Dates: 09/01/14 – 08/31/18

PHARMACEUTICAL INITIATED FUNDING

1. Phase 1b/II trial of pembrolizumab (MK-3475) combination therapies in metastatic castration-resistant prostate cancer (KEYNOTE-365).
Grant amount:
Source: Merck Sharp &Dohme Corp.
Role: Concept and protocol co-developed with Merck and Overall Principal Investigator for international trial
Dates: 01/13/17 – 12/31/23

2. A phase 1b, multicenter, two-part, open label study of DS-8201A, an anti-human epidermal growth factor receptor-2 (HER2)-antibody drug conjugate in combination with nivolumab, an anti PD-1 antibody for subjects with HER2-expressing advanced breast and urothelial cancer.
Grant amount:
Source: Daiichi Sankyo
Role: Site principal investigator
Dates: 01/07/19 – 03/31/23

3. A phase 1, open-label, non-randomized, safety, tolerability, and pharmacokinetic study of TAS3681 in patients with metastatic castration-resistant prostate cancer.
Grant amount:
Source: Taiho
Role: Site principal investigator
Dates: 09/12/19 – 05/31/24

4. An open-label, randomized, controlled phase 3 study of enfortumab vedotin in combination with pembrolizumab with or without chemotherapy, versus chemotherapy alone in previously untreated locally advanced or metastatic urothelial cancer.
Grant amount:
Source: Seattle Genetics, Inc.
Role: Site principal investigator
Dates: 12/10/19 – 04/30/25

5. A phase 1b/2 study of ibrutinib combination therapy in selected advanced gastrointestinal and genitourinary tumors.
Grant amount:
Source: Pharmacyclics, Inc.
Role: Site principal investigator

Dates: 01/06/20 – 09/25/24

6. A phase 3, randomized open-label study of pembrolizumab (MK-3475) plus olaparib versus abiraterone acetate or enzalutamide in participants with metastatic castration-resistant prostate cancer (mCRPC) who are unselected for homologous recombination repair.
   Grant amount:
   Source: Merck Sharp & Dohme Corp.
   Role: Site and overall international principal
   Dates: investigator 01/17/20 – 05/31/24

7. DAROL: Darolutamide observational study in nonmetastatic castration-resistant prostate cancer patients.
   Grant amount:
   Source: Bayer AG
   Role: Site and overall international principal investigator
   Dates: 05/27/20 – 10/14/24

8. A multicenter, randomized, controlled phase 2 study: Efficacy and safety of ^{131}I-1095 radiotherapy in combination with enzalutamide in metastatic castration-resistant prostate cancer patients who are ^{18}F-DCFPyL prostate-specific membrane antigen-avid, chemotherapy-naïve, and progressed on abiraterone (ARROW).
   Grant amount:
   Source: Progenics Pharmaceuticals, Inc.
   Role: Site and overall international principal investigator
   Dates: 06/03/20 – 05/31/24

9. A phase 2 basket study of Tucatinib in combination with trastuzumab in subjects with previously treated, locally-advanced unresectable or metastatic solid tumors driven by HER2 alterations.
   Grant amount:
   Source: Seagen, Inc.
   Role: Site and overall international principal investigator
   Dates: 02/24/21 – 01/31/26

10. A phase 2 trial of SRF617 in combination with AB928 (Etrumadenant) and AB122 (Zimberelimab) in patients with metastatic castration resistant prostate cancer.
    Grant amount:
    Source: Surface Oncology, Inc.
    Role: Site and overall principal investigator
    Dates: 05/17/22 – 01/31/27

PHARMACEUTICAL INITIATED FUNDING: COMPLETED

1. A Phase II multicenter evaluation of the safety and efficacy of Tocosol paclitaxel (s-8184 paclitaxel injectable emulsion) in patients with metastatic or locally advanced unresectable transitional cell carcinoma of the urothelium.
   Grant amount:
   Source: Sonus Pharmaceuticals, Inc.
   Role: Site principal investigator
   Dates: 12/15/04 – 12/15/08

2. A phase II multi-center open-label study of YM155 in subjects with hormone-refractory prostate cancer previously treated with at least one prior chemotherapy regimen.
   Grant amount:
   Source: Astellas Pharma US, Inc.
   Role: Site principal investigator
   Dates: 09/01/07 – 04/30/09

3. Phase II Study of Dasatinib for Androgen-Deprived Progressive Prostate Cancer.
   Grant amount:
   Source: Bristol Myers Squibb Co.
   Role: Overall principal investigator
   Dates: 05/01/07 – 04/01/10

4. A phase 1 study evaluating a second-generation antisense oligonucleotide (OGX-427) that inhibits heat shock protein 27 (HSP27).
   Grant amount:
   Source: OncoGeneX Technologies, Inc.
   Role: Site principal investigator
   Dates: 05/17/07 – 04/30/11

5. A phase III randomized placebo-controlled double-blind study to assess the efficacy and safety of once-daily orally administered ZD4054 10 mg in non-metastatic hormone-resistant prostate cancer patients.
   Grant amount:
   Source: AstraZeneca Pharmaceuticals, LP
   Role: Site principal investigator
   Dates: 04/01/08 – 03/31/11

6. A phase III randomized double-blind placebo-controlled study of abiraterone acetate (CB7630) plus prednisone in patients with metastatic castration-resistant prostate cancer who have failed docetaxel-based chemotherapy.
   Grant amount:
   Source: Cougar Biotechnology
   Role: Site principal investigator
   Dates: 10/1/08 – 09/30/11

7. A randomized double-blind phase III trial comparing docetaxel combined with dasatinib to docetaxel combined with placebo in castration-resistant prostate cancer.
   Grant amount:
   Source: Bristol-Myers Squibb Co.
   Role: Steering committee member and site principal investigator
   Dates: 06/15/09 - 06/14/14

8. A phase 3, randomized, double-blind, placebo-controlled study of abiraterone acetate (CB7630) plus prednisone in asymptomatic or mildly symptomatic patients with metastatic castration-resistant prostate cancer.
   Grant amount:
   Source: Cougar Biotechnology (changed to Janssen)
   Role: Site principal investigator
   Dates: 06/15/09 – 03/16/15

9. A phase II, open-label, single-arm trial evaluating KX2-391 in patients with bone-metastatic, castration-resistant prostate cancer who have not received prior chemotherapy.
   Grant amount:
   Source: Kinex Pharmaceuticals
   Role: Site principal investigator and assistance with protocol development
   Dates: 05/05/10 – 12/19/12

10. A randomized, open-label, phase 2 trial examining the sequencing of sipuleucel-T and androgen deprivation therapy in men with non-metastatic prostate cancer and a rising prostate specific antigen after primary therapy.
    Grant amount:
    Source: Dendreon
    Role: Site principal investigator
    Dates: 11/04/11 – 11/03/15

11. A randomized, double-blind phase 2 study comparing gemcitabine and cisplatin in combination with OGX-427 or placebo in patients with advanced transitional cell carcinoma.
    Grant amount:
    Source: OncoGeneX Technologies, Inc.
    Role: Site principal investigator
    Dates: 02/14/12 – 11/03/15

12. Open label study of the effect of GTx-758 on serum PSA and free testosterone levels in men with castration resistant prostate cancer and maintained on androgen deprivation therapy.
    Grant amount:
    Source: GTx, Inc.
    Role: Overall principal investigator and assistance with protocol development
    Dates: 02/16/12 – 02/27/12

13. An open-label, multicenter, randomized phase 2 study evaluating the safety and efficacy of docetaxel in combination with IMC-1121B or IMC-18F1 or without investigational therapy as second line therapy in patients with metastatic transitional cell carcinoma.
    Grant amount:
    Source: Imclone Systems, Inc.
    Role: Site principal investigator
    Dates: 05/08/12 – 01/14/15

14. Phase II, open label study of the effect of GTx-758 as secondary hormonal therapy on serum PSA and serum free testosterone levels in men with metastatic castration resistant prostate cancer maintained on androgen deprivation therapy.
    Grant amount:
    Source: GTx, Inc.
    Role: Overall principal investigator
    Dates: 12/20/12 – 09/30/15

15. A phase II, multicenter, single-arm study of MPDL3280A in patients with locally advanced or metastatic urothelial bladder cancer.
    Grant amount:
    Source: Genentech/Roche

Role: Site principal investigator
Dates: 08/21/14 – 08/20/16

16. A phase 3, randomized, double-blind, placebo-controlled study of ramucirumab plus docetaxel vs. placebo plus docetaxel in patients with locally advanced or unresectable or metastatic urothelial carcinoma who progressed on or after platinum-based therapy.
Grant amount:
Source: Eli Lilly and Company
Role: Site principal investigator
Dates: 06/21/16 – 07/31/17

17. A multicenter, single-arm, open-label, post-marketing safety study to evaluate the risk of seizure among subjects with metastatic castration-resistant prostate cancer treated with enzalutamide who are at potential increased risk of seizure.
Grant amount:
Source: Astellas, Inc.
Role: Site principal investigator
Dates: 09/12/14 – 09/11/17

18. A phase I study of the safety and pharmacokinetics of escalating doses of AGS15E given as monotherapy in subjects with metastatic urothelial cancer.
Grant amount:
Source: Agensys Inc.
Role: Site principal investigator
Dates: 03/12/14 – 12/31/17

19. A phase II clinical trial of pembrolizumab (MK-3475) in subjects with advanced/unresectable or metastatic urothelial cancer.
Grant amount:
Source: Merck Sharp & Dohme Corp.
Role: Site principal investigator
Dates: 03/22/16 – 03/21/18

20. A phase 2 study of TGF-inhibition (Vactosertib) with Anti-PD-L1 (Durvalumab) in patients with advanced or recurrent urothelial carcinoma failing to achieve response with checkpoint inhibition.
Grant amount:
Source: MedPacto
Role: Site principal investigator
Dates: 09/01/20 – 01/04/21

21. A single-arm, open-label, multicenter study of enfortumab vedotin (ASG-22CE) for treatment of patients with locally advanced or metastatic urothelial cancer who previously received immune checkpoint inhibitor therapy.
Grant amount:
Source: Seattle Genetics, Inc.
Role: Steering committee member and Site principal investigator
Dates: 10/13/17 – 08/31/22

22. A phase 3 randomized, controlled clinical trial of pembrolizumab with or without platinum-based combination chemotherapy vs. chemotherapy in subjects with advanced or metastatic urothelial carcinoma.
Grant amount:
Source: Merck Sharp &Dohme Corp.
Role: Site principal investigator
Dates: 11/16/16 – 11/15/22

REFEREED JOURNALS

1. Yu EY, Meyer GE, Brawer MK. The relation of p53 nuclear accumulation and angiogenesis in human prostatic carcinoma. *Prostate Cancer Prostatic Dis* 1997; 1(1):39-44. PMID: 12496932.

2. Kuo CJ, Farnebo F, Yu EY, Christofferson R, Swearingen RA, Carter R, von Recum HA, Yuan J, Kamihara J, Flynn E, D'Amato R, Folkman J, Mulligan RC. Comparative evaluation of the antitumor activity of antiangiogenic proteins delivered by gene transfer. *Proc Natl Acad Sci* 2001; 98(8):4605-4610. Epub March 27, 2001. PMID: 11274374. PMCID: 31881.

3. [á]Stewart SA, [á]Dykxhoorn DM, [á]Palliser D, Mizuno H, Yu EY, An DS, Sabatini DM, Chen ISY, Hahn WC, Sharp PA, Weinberg RA, Novina CD. Lentivirus-delivered stable gene silencing by RNAi in primary cells. *RNA* 2003; 9(4):493-501. [á]*These authors contributed equally to this work.* PMID: 12649500. PMCID: 1370415.

4. Masutomi K, [á]Yu EY, [á]Khurts S, Ben-Porath I, Currier JL, Metz GB, Brooks MW, Kaneko S, Murakami S, DeCaprio JA, Weinberg RA, Stewart SA, Hahn WC. Telomerase maintains telomere structure in normal human cells. *Cell* 2003; 114(2):241-253. [á]*These authors contributed equally to this work.* PMID: 12887925.

5. Yu EY, Hahn WC. Genetic alterations in prostate cancer. *Clin Prostate Cancer* 2005; 3(4):220-229. PMID: 15882478.

6. Yu EY, Mankoff DM. Positron Emission Tomography (PET) Imaging as a Cancer Biomarker. *Expert Rev Mol Diagn* 2007; 7(5):659-672. PMID: 17892371.

7. Koreckij T, Nguyen H, Brown LG, Yu EY, Vessella RL, Corey E. Dasatinib inhibits the growth of prostate cancer in bone and provides additional protection from osteolysis. *Br J Cancer* 2009; 101(2):263-268. PMID: 19603032. PMCID: 2720213.

8. Perez FA, Fligner CL, Yu EY. Rapid clinical deterioration and leukemoid reaction following treatment of urothelial carcinoma of the bladder: possible role of granulocyte-colony stimulating factor. *J Clin Oncol* 2009; 27(34):e215-217. Epub September 28, 2009. PMID: 19786665.

9. Yu EY, Wilding G, Posadas M, Gross M, Culine S, Massard C, Morris M, Hudes GR, Calabro F, Trudel GC, Sternberg CN. Phase 2 study of dasatinib in patients with metastatic castration-resistant prostate cancer. *Clin Cancer Res* 2009; 15(23):7421-7428. Epub November 17, 2009. PMID: 19920114. PMCID: 3394097. NIHMSID: 340778.

10. Scher HI, Beer TM, Higano CS, Anand A, Taplin ME, Efstathiou E, Rathkopf D, Shelkey J, Yu EY, Alumkal J, Hung D, Hirmand M, Seely L, Morris MJ, Danila DC, Humm J, Larson S, Fleisher M, Sawyers CL. Antitumour activity of MDV3100 in castration-resistant prostate cancer: a phase

1-2 study. *Lancet* 2010; 375(9724):1437-1446. Epub April 14, 2010. PMID: 20398925. PMCID: 2948179. NIHMSID: 207007.

*11. Yu EY, Gulati R, Telesca D, Jiang P, Tam S, Russell KJ, Nelson PS, Etzioni RD, Higano CS. Duration of first off treatment interval is prognostic for time to castration resistance and death in men with biochemical relapse of prostate cancer treated on a prospective trial of intermittent androgen deprivation. *J Clin Oncol* 2010; 28(16):2668-2673. Epub April 26, 2010. PMID: 20421544. PMCID: 2881848.

12. Chi KN, Hotte SJ, Yu EY, Tu D, Eigl B, Tannock I, Saad F, North S, Powers J, Gleave ME, Eisenhauer EA. Randomized phase 2 study of docetaxel and prednisone with or without OGX-011 in patients with metastatic castration resistant prostate cancer. *J Clin Oncol* 2010; 28(27):4247-4254. Epub August 23, 2010. PMID: 20733135.

13. Ermoian R, Kalina R, Yu EY, Parvathaneni U. Ocular prostate cancer metastasis treated with external beam radiation. *Retin Cases Brief Rep* 2011; 5(4):306-308. Epub January 5, 2011. PMID: 25390420.

14. Yu EY, Muzi M, Hackenbracht J, Rezvani BB, Link JM, Montgomery RB, Higano CS, Eary J, Mankoff DA. 1-^{11}C-acetate and ^{18}F-fluorodeoxyglucose positron emission tomography (PET) for men with prostate cancer bone metastases – relative findings and response to therapy. *Clin Nucl Med* 2011; 36(3):192-198. PMID: 21285676. PMCID: 3129631. NIHMSID: 299869.

15. Yu EY, Massard C, Gross M, Carducci M, Culine S, Hudes G, Posadas E, Sternberg C, Wilding G, Trudel G, Paliwal P, Fizazi K. Once-daily dasatinib: Expansion of a phase 2 study evaluating the safety and efficacy of dasatinib in patients with metastatic castration-resistant prostate cancer. *Urology* 2011; 77 (5):1166-1171. PMID: 21539969. PMCID: 3394099. NIHMSID: 340775.

16. [á]Choueiri TK, [á]Ross RW, Jacobus S, Vaishampayan U, Yu EY, Quinn DI, Hahn N, Hutson TE, Sonpavde G, Morrissey SC, Buckle GC, Kim WY, Petrylak DP, Ryan CW, Eisenberger MA, Mortazavi A, Bubley GJ, Taplin ME, Rosenberg JE, Kantoff PW. A double blind randomized trial of docetaxel + vandetanib vs. docetaxel + placebo in platinum-pretreated metastatic urothelial cancer. *J Clin Oncol* 2011; 10(5):507-512. Epub December 19, 2011. [á]*These authors contributed equally to this work.* PMID: 22184381. PMCID: 4104290.

*17. Yu EY, Kuo KF, Gulati R, Chen S, Gambol TE, Hall SP, Jiang PY, Pitzel P, Higano CS. Long-term dynamics of bone mineral density during intermittent androgen deprivation for men with non-metastatic, hormone-sensitive prostate cancer. *J Clin Oncol* 2012; 30(15):1864-1870. Epub April 9, 2012. PMID: 22493411. PMCID: 3383183.

*18. Yu EY, Miller K, Nelson J, Gleave M, Fizazi K, Moul JW, Nathan FE, Higano CS. Detection of previously unidentified metastatic disease as a leading cause of screening failure in a Phase III trial of zibotentan versus placebo in patients with non-metastatic castration-resistant prostate cancer. *J Urol* 2012; 188(1):103-109. Epub May 12, 2012. PMID: 22583636. PMCID: 3473078. NIHMSID: 401806.

19. Ryan CJ, Smith MR, de Bono JS, Molina A, Logothetis CJ, de Souza P, Fizazi K, Mainwaring P, Piulats JM, Ng S, Carles J, Mulders PFA, Basch E, Small EJ, Saad F, Schrijvers D, Van Poppel H, Mukherjee SD, Suttmann H, Gerritsen WR, Flaig TW, George DJ, Yu EY, Efstathiou E, Pantuck A,

Winquist E, Higano CS, Taplin ME, Park Y, Kheoh T, Griffin T, Scher HI, Rathkopf DE. Abiraterone in metastatic prostate cancer with no prior chemotherapy. *N Engl J Med* 2013; 368(2):138-148. Epub December 10, 2012. PMID: 23228172. NIHMSID: 472275.

20. Antonarakis ES, Heath EI, Posadas EM, Yu EY, Harrison MR, Bruce JY, Cho SY, Wilding GE, Fetterly GJ, Hangauer DG, Kwan MR, Dyster LM, Carducci MA. A phase 2 study of KX2-391, an oral inhibitor of SRC kinase and tubulin polymerization, in men with bone metastatic castration-resistant prostate cancer. *Cancer Chemother Pharmacol* 2013; 71(4):883-892. Epub January 13, 2013. PMID: 23314737. PMCID: 3609871. NIHMSID: 435432.

21. Araujo JC, Trudel GC, Saad F, Armstrong A, Yu EY, Bellmunt J, Wilding G, McCaffrey J, Serrano SV, Matveev V, Efstathiou E, Oudard S, Morris MJ, Sizer B, Goebell PJ, Heidenreich A, de Bono JS, Begbie S, Hong JH, Richardet E, Gallardo E, Paliwal P, Durham S, Cheng S, Logothetis C. Docetaxel and dasatinib or placebo in men with metastatic castration-resistant prostate cancer (READY): a randomised, double-blind phase 3 trial. *Lancet Oncol* 2013; 14(13):1307-1316. Epub November 8, 2013. PMID: 24211163. PMCID: 5478530.

22. Mossanen M, Lee F, Cheng HH, Harris WP, Shenoi J, Zhao S, Wang JF, Champion T, Izard J, Gore JL, Porter MP, Yu EY, Wright JL. Non-response to neoadjuvant chemotherapy for muscle invasive urothelial carcinoma of the bladder. *Clin Genitourin Cancer* 2014; 12(3):210-213. Epub November 12, 2013. PMID: 24361053.

23. Lee FC, Harris W, Cheng HH, Shenoi J, Zhao S, Wang JF, Champion T, Izard J, Gore JL, Porter M, Yu EY, Wright JL. Pathologic response rates of gemcitabine/cisplatin vs. methotrexate/vinblastin/adriamycin/cisplatin neoadjuvant chemotherapy for muscle invasive urothelial bladder cancer. *Adv Urol* 2013; 2013:317190. Epub December 8, 2013. PMID: 24382958. PMCID: 3871504.

24. Crawford ED, Stone NN, Yu EY, Koo PJ, Freedland SJ, Slovin SF, Gomella LG, Berger ER, Keane TE, Sieber P, Petrylak DP. Challenges and recommendations for early identification of metastatic disease in prostate cancer. *Urology* 2014; 83(3):664-669. Epub January 8, 2014. PMID: 24411213.

25. James AC, Lee FC, Izard JP, Harris WP, Cheng HH, Zhao S, Gore JL, Lin DW, Porter MP, Yu EY, Wright JL. Role of maximal endoscopic resection prior to cystectomy for invasive urothelial bladder cancer. *Clin Genitourin Cancer* 2014; 12(4):287-291. Epub January 23, 2014. PMID: 24560087.

26. Rathkopf DE, Smith MR, de Bono JS, Logothetis CJ, Shore ND, de Souza P, Fizazi K, Mulders PF, Mainwaring P, Hainsworth JD, Beer TM, North S, Fradet Y, Van Poppel H, Carles J, Flaig TW, Efstathiou E, Yu EY, Higano CS, Taplin ME, Griffin TW, Todd MB, Yu MK, Park YC, Kheoh T, Small EJ, Scher HI, Molina A, Ryan CJ, Saad F. Updated interim efficacy analysis and long-term safety of abiraterone acetate in metastatic castration-resistant prostate cancer patients without prior chemotherapy (COU-AA-302). *Eur Urol* 2014; 66(5):815-825. Epub March 6, 2014. PMID: 24647231. PMCID: 4418928. NIHMSID: 620764.

27. Hussain M, Daignault S, Agarwal N, Grivas PE, Siefker-Radtke AO, Puzanov I, MacVicar GR, Levine EG, Srinivas S, Twardowski P, Eisenberger MA, Quinn DI, Vaishampayan UN, Yu EY, Dawsey S, Day KC, Day ML, Al-Hawary M, Smith DC. A randomized phase II trial of gemcitabine/cisplatin with or without cetuximab in patients with advanced urothelial

carcinoma. *Cancer* 2014; 120(17):2684-2693. Epub May 6, 2014. PMID 24802654. PMCID: 4142676. NIHMSID: 615329.

28. Yu EY, Getzenberg RH, Coss CC, Gittelman MM, Keane T, Tutrone R, Belkoff L, Given R, Bass J, Chu F, Gambla M, Gaylis F, Bailen J, Hancock ML, Smith J, Dalton JT, Steiner MS. Selective ER alpha agonist, GTx-758, decreases testosterone with reduced side effects of androgen deprivation therapy in men with advanced prostate cancer. *Eur Urol* 2015; 67(2):334-341. Epub June 24, 2014. PMID: 24968970.

29. Kuo KF, Hunter-Merrill R, Gulati R, Hall SP, Gambol TE, Higano CS, Yu EY. Relationships between times to testosterone and prostate-specific antigen rises during the first "off treatment" interval of intermittent androgen deprivation are prognostic for castration-resistance in men with non-metastatic prostate cancer. *Clin Genitourin Cancer* 2015; 13(1): 10-16. Epub August 10, 2014. PMID: 25242417. PMCID: 4289425. NIHMSID: 629851.

30. Zargar H, Espiritu PN, Fairey AS, Mertens L, Dinney CP, Mir MC, Krabbe LM, Cookson MS, Jacobsen NE, Gandhi N, Griffin J, Montgomery JS, Vasdev N, Yu EY, Youssef D, Xylinas E, Campain NJ, Kassouf W, Dall'Era MA, Seah JA, Ercole CE, Horenblas S, Sridhar SS, McGrath JS, Aning J, Shariat SF, Wright JL, Thorpe AC, Morgan TM, Holzbeierlein JM, Bivalacqua TJ, North S, Barocas DA, Lotan Y, Garcia JA, Stephenson AJ, Shah JB, van Rhijn BW, Daneshmand S, Spiess PE, Black P. Multicenter assessment of neoadjuvant chemotherapy for muscle-invasive bladder cancer. *Eur Urol* 2015; 67(2):241-249. Epub September 23, 2014. PMID: 25257030. PMCID: 4840190.

31. Chevillet JR, Kang Q, Ruf IK, Briggs HA, Vojtech LN, Hughes SM, Cheng HH, Arroyo JD, Meredith EK, Gallichotte EN, Pogosova-Agadjanyan EL, Vessella RL, Stirewalt DL, Hladik F, Yu EY, Higano CS, Tewari M. Quantitative and stoichiometric analysis of the microRNA content of exosomes. *Proc Natl Acad Sci* 2014; 111(41):14888-14893. Epub September 29, 2014. PMID: 25267620. PMCID: 4205618.

32. Cheng HH, Gulati R, Azad A, Nadal R, Twardowski P, Vaishampayan UN, Agarwal N, Heath EI, Pal SK, Rehman H, Leiter A, Batten JA, Montgomery RB, Galsky MD, Antonarakis ES, Chi KN, Yu EY. Activity of enzalutamide in men with metastatic castration resistant prostate cancer is affected by prior treatment with abiraterone and/or docetaxel. *Prostate Cancer Prostatic Dis* 2015; 18(2):122-127. Epub January 20, 2015. PMID: 25600186. PMCID: 4430366. NIHMSID: 643944.

*33. Yu EY, Duan F, Muzi M, Deng X, Chin BB, Alumkal JJ, Taplin ME, Taub JM, Herman B, Higano CS, Doot RK, Hartfeil D, Febbo PG, Mankoff DA. Castration-resistant prostate cancer bone metastasis response measured by ^{18}F-fluoride PET after treatment with dasatinib and correlation with progression-free survival: Results from ACRIN 6687. *J Nucl Med* 2015; 56(3):354-360. Epub January 29, 2015. PMID: 25635138. PMCID: 4410847. NIHMSID: 679024.

34. Izard JP, Gore JL, Mostaghel EA, Wright JL, Yu EY. Persistent, unexplained leukocytosis is a paraneoplastic syndrome associated with poor prognosis in patients with urothelial carcinoma. *Clin Genitourin Cancer* 2015; 13(4):e253-e258. Epub March 15, 2015. PMID: 25882979.

*35. Yu EY, Li H, Higano CS, Agarwal N, Pal SK, Alva A, Heath EI, Lam ET, Gupta S, Lilly MB, Inoue Y, Chi KN, Vogelzang NJ, Quinn DI, Cheng HH, Plymate SR, Hussain M, Tangen CM, Thompson IM Jr. SWOG S0925: A randomized phase 2 study of androgen deprivation combined with cixutumumab versus androgen deprivation alone in patients with new metastatic hormone-sensitive prostate cancer. *J Clin Oncol* 2015; 33(14):1601-1608. Epub April 6, 2015. PMID: 25847934. PMCID: 4417730.

36. Galsky MD, Pal SK, Chowdhury S, Harshman LC, Crabb SJ, Wong Y, Yu EY, Powles T, Moshier EL, Ladoire S, Hussain SA, Agarwal N, Vaishampayan U, Recine F, Berthold D, Necchi A, Theodore C, Milowsky MI, Bellmunt J, Rosenberg JE, RISC. Comparative effectiveness of gemcitabine plus cisplatin versus methotrexate, vinblastine, doxorubicin, plus cisplatin as neoadjuvant therapy therapy for muscle-invasive bladder cancer. *Cancer* 2015; 121(15):2586-2593. Epub April 14, 2015. PMID: 25872978.

37. Cheng HH, Soleau C, Yu EY. Improved disease markers suggest dual response in a patient with metastatic castration resistant prostate cancer and chronic lymphocytic leukemia following active cellular immunotherapy. *J Hematol Oncol* 2015; 8:51. Epub May 14, 2015. PMID: 25966929. PMCID: 4440265.

38. Robinson D, Van Allen EM, Wu YM, Schultz N, Lonigro RJ, Mosquera JM, Montgomery RB, Taplin ME, Pritchard CC, Attard G, Beltran H, Abida WM, Bradley RK, Vinson J, Cao X, Vats P, Kunju LP, Hussain M, Feng FY, Tomlins SA, Cooney KA, Smith DC, Brennan C, Siddiqui J, Mehra R, Chen Y, Rathkopf DE, Morris MJ, Solomon SB, Durack JC, Reuter VE, Gopalan A, Gao J, Loda M, Lis RT, Bowden M, Balk SP, Gaviola G, Sougnez C, Gupta M, Yu EY, Mostaghel EA, Cheng HH, Mulcahy H, True LD, Plymate SR, Dvinge H, Ferraldeschi R, Flohr P, Miranda S, Zafeiriou Z, Tunariu N, Mateo J, Lopez RP, Demichelis F, Elemento O, Robinson BD, Sboner A, Schiffman MA, Nanus DM, Tagawa ST, Sigaras A, Eng KW, Heath E, Scher HI, Pienta KJ, Kantoff PW, de Bono JS, Rubin MA, Nelson PS, Garraway LA, Sawyers CL, Chinnaiyan AM. Integrative clinical genomics of advanced prostate cancer. *Cell* 2015; 161(5):1215-1228. Epub May 21, 2015. PMID: 26000489. PMCID: 4484602. NIHMSID: 702018.

39. Zargar H, Zargar-Shoshtari K, Lotan Y, Shah JB, van Rhijn BW, Daneshmand S, Spiess PE, Black Pl; Collaborators (Fairey AS, Mertens LS, Horenblas S, Dinney CP, Mir MC, Ercole CE, Stephenson AJ, Krabbe LM, Cookson MS, Jacobsen NE, Barocas D, Griffin J, Holzbeierlein JM, Montgomery JS, Morgan TM, Vasdev N, Thorpe AC, Aning J, Yu EY, Wright JL, Xylinas E, Campain NJ, Pourmalek F, McGrath JS, Kassouf W, Dall'Era MA, Seah JA, Sridhar SS, Sharma P, Shariat SF, North S, Grivas P, Gandhi N, Bivalacqua TJ). Final pathological stage after neoadjuvant chemotherapy and radical cystectomy for bladder cancer - does pT0 predict better survival than pTa/pTis/pT1? *J Urol* 2016; 195(4P1):886-893. Epub October 20, 2015. PMID: 26521718.

40. Petrylak DP, Tagawa ST, Kohli M, Eisen A, Canil C, Sridhar SS, Spira A, Yu EY, Burke JM, Shaffer D, Pan CX, Kim JJ, Aragon-Ching JB, Quinn DI, Vogelzang NJ, Tang S, Zhang H, Cavanaugh CT, Gao L, Kauh JS, Walgren RA, Chi KN. Docetaxel monotherapy or combined with ramucirumab or icrucumab in second-line locally advanced or metastatic urothelial carcinoma: an open-label, three-arm, randomized controlled phase II trial. *J Clin Oncol* 2016; 34(13):1500-1509. Epub February 29, 2016. PMID: 26926681.

41. Chi KN, Yu EY, Jacobs C, Bazov J, Kollmannsberger C, Higano CS, Mukherjee S, Gleave M, Stewart P, Hotte S. A phase 1 dose-escalation study of Apatorsen (OGX-427), an antisense

inhibitor targeting heat shock protein 27 (HSP27), in patients with castration resistant prostate cancer and advanced cancers. *Ann Oncol* 2016; 27(6):1116-1122. Epub February 18, 2016. PMID: 27022067.

42. [á]Kumar A, [á]Coleman I, Morrissey C, Zhang X, True LD, Gulati R, Etzioni R, Bolouri H, Montgomery B, White T, Lucas JM, Brown LG, Dumpit RF, DeSarkar N, Higano CS, Yu EY, Coleman R, Schultz N, Fang M, Lange PH, Shendure J, Vessella RL, Nelson PS. Substantial inter-individual and limited intra-individual genomic diversity among tumors from men with metastatic prostate cancer. *Nat Med* 2016; 22(4):369-378. Epub February 29, 2016. [á]*These authors contributed equally to this work.* PMID: 26928463. PMCID: 5045679. NIHMSID: 756732.

43. Schweizer MT, Gulati R, Mostaghel E, Nelson PS, Montgomery RB, Yu EY, Cheng HH. Docetaxel-related toxicity in metastatic hormone-sensitive and metastatic castration-resistant prostate cancer. *Med Oncol* 2016; 33(7):77. Epub June 14, 2016. PMID: 27300548. PMCID: 5298886. NIHMSID: 847321.

44. Cheng HH, Klemfuss NM, Montgomery B, Higano CS, Schweizer MT, Mostaghel EA, McFerrin L, Yu EY, Nelson PS, Pritchard CC. A pilot study of clinical targeted next generation sequencing for prostate cancer: consequences for treatment and genetic counseling. *Prostate* 2016; 76(14):1303-1311. Epub June 21, 2016. PMID: 27324988. PMCID: 5549853. NIHMSID: 888786.

45. Ramos JD, Casey MF, Bamias A, De Giorgi U, Bellmunt J, Harshman LC, Ladoire S, Wong YN, Alva AS, Rosenberg J, Galsky MD, Yu EY, RISC Investigators. The Khorana score in predicting venous thromboembolism for patients with metastatic urothelial carcinoma and variant histology treated with chemotherapy. *Clin Appl Thromb Hemost* 2016; Epub September 16, 2016. PMID: 27637910. PMCID: 5685501.

46. Necchi A, Sonpavde G, Lo Vullo S, Giardiello D, Bamias A, Crabb SJ, Harshman LC, Bellmunt J, De Giorgi U, Sternberg CN, Cerbone L, Ladoire S, Wong YN, Yu EY, Chowdhury S, Niegisch G, Srinivas S, Vaishampayan UN, Pal SK, Agarwal N, Alva A, Baniel J, Golshayan A, Morales-Barrera R, Bowles D, Milowsky MI, Theodore C, Berthold RD, Daugaard G, Sridhar SS, Powles T, Rosenberg JE, Galsky MD, Mariani L, RISC Investigators. Nomogram-based prediction of overall survival in patients with metastatic urothelial carcinoma receiving first-line platinum-based chemotherapy: Retrospective International Study of invasive/advanced cancer of the urothelium (RISC). *Eur Urol* 2017; 71(2):281-289. Epub October 7, 2016. PMID: 27726966. PMCID: 5576985. NIHMSID: 896015.

47. Schweizer MT, Cheng HH, Tretiakova MS, Vakar-Lopez F, Klemfuss N, Mostaghel EA, Nelson PS, Yu EY, Montgomery RB, True LD, Pritchard CC. Mismatch repair deficiency is common in ductal prostatic adenocarcinoma. *Oncotarget* 2016; 7(50):82504-82510. Epub October 15, 2016. PMID: 27756888. PMCID: 5347709.

48. Rose TL, Deal AM, Ladoire S, Crehange G, Galsky MD, Rosenberg JE, Bellmunt J, Wimalasingham A, Wong YN, Harshman LC, Chowdhury S, Niegisch G, Liontos M, Yu EY, Pal SK, Chen RC, Wang AZ, Nielsen ME, Smith AB, Milowsky MI; RISC Investigators. Patterns of bladder preservation therapy utilization for muscle-invasive bladder cancer. *Bladder Cancer* 2016; 2(4):405-413. Epub October 27, 2016. PMID: 28035321. PMCID: 5181658.

49. Antonarakis EA, Kibel AS, Yu EY, Karsh LI, Elfiky A, Shore ND, Vogelzang NJ, Corman JM, Millard FE, Maher JC, Chang N, DeVries T, Sheikh NA, Drake CG. Sequencing of sipuleucel-T and androgen deprivation therapy in men with hormone-sensitive biochemically-recurrent prostate cancer: A phase II randomized trial. *Clin Cancer Res* 2017; 23(10):2451-2459. Epub November 10, 2016. PMID: 27836866.

50. Balar AV, Galsky MD, Rosenberg JE, Powles T, Petrylak DP, Bellmunt J, Loriot Y, Necchi A, Hoffman-Censits J, Perez-Gracia JL, Dawson NA, van der Heijden MS, Dreicer R, Srinivas S, Retz MM, Joseph RW, Drakaki A, Vaishampayan U, Sridhar SS, Quinn DI, Duran I, Shaffer DR, Eigl BJ, Grivas PD, Yu EY, Li S, Kadel EE, Boyd Z, Bourgon R, Hegde PS, Mariathasan S, Thastrom AC, Abidoye OO, Fine GD, Bajorin DF. Atezolizumab as first-line therapy in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicenter, phase 2 trial. *Lancet* 2017; 389(10064):67-76. Epub December 7, 2016. PMID: 27939400. PMCID: 5568632. NIHMSID: 896050.

51. Alva A, Nordquist L, Daignault S, George S, Ramos J, Albany C, Isharwal S, McDonald M, Campbell G, Danchaivijitr P, Yentz S, Anand A, Yu EY. Clinical correlates of benefit from radium-223 therapy in metastatic castration resistant prostate cancer. *Prostate* 2016; 77(5):479-488. Epub December 19, 2016. PMID: 27990667.

52. [á]Ramos JD, [á]Casey MF, Crabb SJ, Bamias A, Harshman LC, Wong YN, Bellmunt J, De Giorgi U, Ladoire S, Powles T, Pal SK, Niegisch G, Recine F, Alva A, Agarwal N, Necchi A, Vaishampayan UN, Rosenberg J, Galsky MD, Yu EY, RISC Investigators. Venous thromboembolism in metastatic urothelial carcinoma and variant histologies: incidence, associative factors and effect on survival. *Cancer Med* 2016; 6(1):186-194. Epub December 20, 2016. PMID: 28000388. PMCID: 5269690. [á]These *authors contributed equally to this work*.

53. Crawford ED, Petrylak DP, Shore N, Saad F, Slovin SF, Vogelzang NJ, Keane TE, Koo PJ, Gomella LG, O'Sullivan JM, Tombal B, Concepcion RS, Sieber P, Stone NN, Finkelstein SE, Yu EY, Prostate Cancer Radiographic Assessments for Detection of Advanced Recurrence (RADAR II) Group. The role of therapeutic layering in optimizing treatment for patients with castration-resistant prostate cancer (RADAR II). *Urology* 2017; 104:150-159. Epub March 14, 2017. PMID: 28302580.

54. Armstrong AJ, Halabi S, Healy P, Alumkal J, Winters C, Kephart J, Bitting RL, Hobbs C, Soleau CF, Beer TM, Slottke R, Mundy K, Yu EY, George D. Phase 2 trial of the PI3 kinase inhibitor buparlisib (BKM-120) with or without enzalutamide in men with metastatic castration resistant prostate cancer. *Eur J Cancer* 2017; 81:228-236. Epub May 11, 2017. PMID: 28502694. PMCID: 6345641. NIHMSID: 1001360.

55. Bose R, Karthaus WR, Armenia J, Abida W, Iaquinta PJ, Zhang Z, Wongvipat J, Wasmuth EV, Shah N, Sullivan PS, Doran MG, Wang P, Patruno A, Zhao Y; International SU2C/PCF Prostate Cancer Dream Team (Robinson D, Van Allen EM, Wu YM, Schultz N, Lonigro RJ, Mosquera JM, Montgomery RB, Taplin ME, Pritchard CC, Attard G, Beltran H, Abida WM, Bradley RK, Vinson J, Cao X, Vats P, Kunju LP, Hussain M, Feng FY, Tomlins SA, Cooney KA, Smith DC, Brennan C, Siddiqui J, Mehra R, Chen Y, Rathkopf DE, Morris MJ, Solomon SB, Durack JC, Reuter VE, Gopalan A, Gao J, Loda M, Lis RT, Bowden M, Balk SP, Gaviola G, Sougnez C, Gupta M, Yu EY, Mostaghel EA, Cheng HH, Mulcahy H, True LD, Plymate SR, Dvinge H, Ferraldeschi R, Flohr P, Miranda S, Zafeiriou Z, Tunariu N, Mateo J, Lopez RP, Demichelis F, Elemento O, Robinson BD, Sboner A, Schiffman MA, Nanus DM, Tagawa ST, Sigaras A, Eng KW, Heath E, Scher HI, Pienta

KJ, Kantoff PW, de Bono JS, Rubin MA, Nelson PS, Garraway LA, Sawyers CL, Chinnaiyan AM), Zheng D, Schultz N, Sawyers CL. ERF mutations reveal a balance of ETS factors controlling prostate oncogenesis. *Nature* 2017; 546(7660):671-675. Epub June 14, 2017. PMID: 28614298. PMCID: 5576182. NIHMSID: 895975.

56. Necchi A, Pond GR, Smaldone MC, Pal SK, Chan K, Wong YN, Viterbo R, Sonpavde G, Harshman LC, Crabb S, Alva A, Chowdhury S, De Giorgi U, Srinivas S, Agarwal N, Bamias A, Baniel J, Golshayan A, Ladoire S, Sternberg CN, Cerbone L, Yu EY, Bellmunt J, Vaishampayan U, Niegisch G, Hussain S, Bowles DW, Morales-Barrera R, Milowsky MI, Theodore C, Berthold RD, Sridhar SS, Powles T, Rosenberg JE, Galsky MD. Robot-assisted versus open radical cystectomy in patients receiving perioperative chemotherapy for muscle-invasive bladder cancer: the oncologists' perspective from a multicenter study. *Eur Urol Focus* 2017; pii: S2405-4569(17)30079-2. Epub March 31, 2017. PMID: 28753879. PMCID: 5626651. NIHMSID: 901370.

57. Necchi A, Mariani L, Lo Vullo S, Yu EY, Woods ME, Pahm M, Wong YN, Harshman LC, Alva A, Sternberg CN, F. Recine, Bamias A, Grivas P, Koshkin VS, Roghmann F, Dobruch J, Eigl B, Nappi L, Milowsky MI, Niegisch G, Pal SK, De Giorgi U, Vaishampayan U, Berthold RD, Bowles DW, Baniel J, Theodore C, Ladoire S, Srinivas S, Agarwal N, Crabb S, Sridhar SS, Golshayan A, Ohlmann C, Xylinas E, Powles T, Rosenberg J, Bellmunt J, Galsky MD, Hendricksen K. Lack of effectiveness of postchemotherapy lymphadenectomy in bladder cancer patients with clinical evidence of metastatic pelvic or retroperitoneal lymph nodes only: a propensity score-based analysis. *Eur Urol Focus* 2017; pii: S2405-4569(17)30125-6. Epub June 3, 2017. PMID: 28753897. PMCID: 5712487. NIHMSID: 901371.

58. Boustani J, Bertaut A, Galsky M, Rosenberg JE, Bellmunt J, Powles T, Wong YN, Recine F, Harshman LC, Chowdhury S, Niegish G, Liontos M, Yu EY, Pal SK, Moshier E, de Giorgi U, Crabb SJ, Milowsky MI, Ladoire S, Créhange G, Retrospective International Study of Cancers of the Urothelial Tract (RISC) Investigators. Radical cystectomy or bladder preservation with radiochemotherapy in elderly patients with muscle-invasive bladder cancer: Retrospective International Study of Cancers of the Urothelial Tract (RISC) Investigators. *Acta Oncol* 2018; 57(4):491-497. Epub August 30, 2017:1-7. PMID: 28853615.

59. Ramos JD, Wingate JT, Gulati R, Plimack ER, Harshman LC, Powles T, Crabb SJ, Niegisch G, Bellmunt J, Ladoire S, De Giorgi U, Hussain S, Alva AS, Baniel J, Agarwal N, Rosenberg JE, Vaishampayan U, Galsky MD, Yu EY, RISC Investigators. Venous thromboembolism risk in patients with locoregional urothelial tract tumors. *Clin Genitourin Cancer* 2017; pii: S1558-7673(17)30242-2. Epub August 24, 2017. PMID: 28923700. PMCID: 5826750. NIHMSID: 917612.

60. Petrylak DP, De Wit R, Chi KN, Drakaki A, Sternberg CN, Nishiyama H, Castellano D, Hussain S, Flechon A, Bamias A, Yu EY, van der Heijden MS, Matsubara N, Alekseev B, Necchi A, Geczi L, Ou YC, Coskun HS, Su WP, Hegemann M, Percent IJ, Lee JL, Tucci M, Semenov A, Laestadius F, Peer A, Tortora G, Safina S, Garcia del Muro X, Rodriguez-Vida A, Cicin I, Harputluoglu H, Widau RC, Liepa AM, Walgren RA, Hamid O, Zimmermann AH, Bell-McGuinn KM, Powles T, RANGE Investigators. Ramucirumab plus docetaxel versus placebo plus docetaxel in patients with locally advanced or metastatic urothelial carcinoma after platinum-based therapy (RANGE): a randomised, double-blind, phase 3 trial. *Lancet* 2017; 390(10109):2266-2277. Epub September 12, 2017. PMID: 28916371.

61. Bamias A, Tzannis K, Harshman LC, Crabb S, Wong YN, Pal SK, De Giorgi U, Ladoire S, Agarwal N, Yu EY, Niegisch G, Necchi A, Sternberg CN, Srinivas S, Alva A, Vaishampayan U, Cerbone L, Liontos M, Rosenberg J, Powles T, Belmunt J, Galsky M, RISC Investigators. Impact of contemporary patterns of chemotherapy utilization on survival in patients with advanced cancer of the urinary tract: a Retrospective International Study of Invasive/advanced Cancer of the urothelium (RISC). *Ann Oncol* 2018; 29(2):361-369. Epub October 25, 2017. PMID: 29077785. PMCID: 7360142.

62. Cheng HH, Plets M, Li H, Higano CS, Tangen CM, Agarwal N, Vogelzang NJ, Hussain M, Thompson IM Jr, Tewari M, Yu EY. Circulating microRNAs and treatment response in SWOG S0925, a randomized phase II study of androgen deprivation combinated with cixutumumab versus androgen deprivation alone for patients with new metastatic hormone-sensitive prostate cancer. *Prostate* 2018; 78(2):121-127. Epub November 6, 2017. PMID: 29105802. PMCID: 5728359. NIHMSID: 920426.

63. Schweizer MT, Hancock ML, Getzenberg RH, Yu EY. Hormone levels following surgical and medical castration: Defining optimal androgen suppression. *Asian J Androl* 2018; 20(4):405-406. Epub November 7, 2017. PMID: 29111538. PMCID: 6038162.

64. Necchi A, Pond GR, Pal SK, Agarwal N, Bowles DW, Plimack ER, Yu EY, Ladoire S, Baniel J, Crabb S, Niegisch G, Sridhar SS, Berthold RD, Rosenberg J, Powles T, Bamias A, Harshman LC, Bellmunt J, Galsky MD. Bone metastases as the only metastatic site in patients with urothelial carcinoma: focus on a special patient population. *Clin Genitourin Cancer* 2018; 16(2):e483-e490. Epub November 1, 2017. PMID: 29158079. PMCID: 7974827. NIHMSID: 1676217.

65. Yu EY, Ellard SL, Hotte SJ, Gingerich JR, Joshua AM, Gleave ME, Chi KN. A randomized phase 2 study of a HSP27 targeting antisense, apatorsen with prednisone versus prednisone alone, in patients with metastatic castration resistant prostate cancer. *Invest New Drugs* 2018; 36(2):278-287. Epub December 18, 2017. PMID: 29250742.

66. Ramos JD, Mostaghel EA, Pritchard CC, Yu EY. DNA repair pathway alterations in metastatic castration-resistant prostate cancer responders to Radium-223. *Clin Genitourin Cancer* 2018; 16(2):106-110. Epub December 6, 2017. PMID: 29287968.

67. Harshman LC, Tripathi A, Kaag M, Efstathiou JA, Apolo AB, Hoffman-Censits JH, Stadler WM, Yu EY, Bochner BH, Skinner EC, Downs T, Kiltie AE, Bajorin DF, Khurshid G, Shipley WU, Steinberg GD, Hahn NM, Shridhar SS. Contemporary patterns of multidisciplinary care in patients with muscle-invasive bladder cancer. *Clin Genitourin Cancer* 2018; 16(3):213-218. Epub December 6, 2017. PMID: 29289519. PMCID: 6731031.

68. Zargar H, Shah JB, van Rhijn BW, Daneshmand S, Bivalacqua TJ, Spiess PE, Black PC, Kassouf W; collaborators (Fransen van de Putte EE, Horenblas S, Potvin KR, Winquist E, Seah JA, Sridhar SS, Jacobsen NE, Zargar-Shoshtari K, Holzbeierlein JM, Griffin J, Dinney C, Krabbe LM, Lotan Y, Kovac E, Ercole CE, Stephenson AJ, Cookson MS, Baras A, Montgomery JS, Morgan TM, Vasdev N, Thorpe AC, Campain NJ, McGrath JS, Yu EY, Wright JL, Xylinas E, Dall'Era MA, Barocas DA, Fairey AS, Shariat SF, Aning J. Neoadjuvant dose dense MVAC versus gemcitabine and cisplatin in patients with cT3-4aN0M0 bladder cancer treated with radical cystectomy. *J Urol* 2018; 199(6):1452-1458. Epub January 9, 2018. PMID: 29329894.

69. Jacene H, Gomella L, Yu EY, Rohren EM. Hematologic toxicity from radium-223 therapy for bone metastases in castration-resistant prostate cancer: risk factors and practical considerations. *Clin Genitourin Cancer* 2018; 16(4):e919-e926. Epub March 23, 2018. PMID: 29678471.

70. Schweizer MT, Haugk K, McKiernan JS, Gulati R, Cheng HH, Maes JL, Dumpit RF, Nelson PS, Montgomery B, McCune JS, Plymate SR, Yu EY. A phase I study of niclosamide in combination with enzalutamide in men with castration-resistant prostate cancer. *PLoS One* 2018; 13(6):e0198389. Epub June 1, 2018. PMID: 29856824. PMCID: 5983471.

71. Vasdev N, Zargar H, Noël JP, R Veeratterapillay, Fairey AS, Mertens LS, Dinney CP, Mir MC, Krabbe LM, Cookson MS, Jacobsen NE, Gandhi NM, Griffin J, Montgomery JS, Yu EY, Xylinas E, Campain NJ, Kassouf W, Dall'Era MA, Seah JA, Ercole CE, Horenblas S, Sridhar SS, McGrath JS, Aning J, Shariat SF, Wright JL, Morgan TM, Bivalacqua TJ, North S, Barocas DA, Lotan Y, Grivas, P, Stephenson AJ, Shah JB, van Rhijn BW, Daneshmand S, Spiess PE, Holzbeierlein JM, Thorpe A, Black PC. Concomitant CIS on TURBT does not impact oncological outcome in patients treated with neoaduvant chemotherapy followed by radical cystectomy. *World J Urol* 2019; 37(1):165-172. Epub June 7, 2018. PMID: 29882105.

72. Lim DM, Gulati R, Aleshin-Guendel S, Gawne AM, Wingate JT, Cheng HH, Etzioni RD, Yu EY. Undetectable prostate-specific antigen after short-course androgen deprivation therapy for biochemically-recurrent prostate cancer patients correlates with metastasis-free survival and prostate cancer-specific survival. *Prostate* 2018; Epub July 10, 2018. PMID: 29987912. PMCID: 6328347. NIHMSID: 981545.

73. Sonpavde GP, Mariani L, Lo Vullo S, Raggi D, Giannatempo P, Bamias A, Crabb SJ, Bellmunt J, Yu EY, Niegisch G, Vaishampayan UN, Theodore C, Berthold DR, Srinivas S, Sridhar SS, Plimack ER, Rosenberg JE, Powles T, Galsky M, Necchi A. Impact of number of cycles of platinum-based first-line chemotherapy for advanced urothelial carcinoma. *J Urol* 2018; 200(6):1207-1214. Epub July 13, 2018. PMID: 30012366. PMCID:6814293.

74. Crawford ED, Koo PJ, Concepcion RS, Freedland SJ, Gomella LG, Karsh L, Keane TE, Maroni P, Penson D, Petrylak DP, Ross A, Shore N, Slovin SF, Divgi C, Mouraviev V, Reiter RE, Yu EY as the Prostate Cancer **R**adiographic **A**ssessments for **D**etection of **A**dvanced **R**ecurrence (RADAR III) Group. A clinician's guide to next generation imaging in patients with advanced prostate cancer (RADAR III). *J Urol* 2019; 201(4):682-692. Epub August 2, 2018. PMID: 30077557.

75. Necchi A, Pond GR, Moschini M, Plimack ER, Niegisch G, Yu EY, Bamias A, Agarwal N, Vaishampayan U, Theodore C, Sridhar SS, Sternberg CN, Powles T, Rosenberg JE, Bellmunt J, Gallina A, Colombo R, Montorsi F, Briganti A, Galsky MD. Development of a prediction tool for exclusive locoregional recurrence after radical cystectomy in patients with muscle-invasive bladder cancer. *Clin Genitourin Cancer* 2019; 17(1):7-14.e3. Epub September 13, 2018. PMID: 30292628. PMCID: 6857172.

76. Yu EY, Gillessen S, Mottet N. What do the guidelines say for metastatic prostate cancer starting androgen deprivation therapy? NCCN, ESMO and EAU recommendations. *Eur Urol Focus* 2019; 5(2):162-164. Epub October 1, 2018. PMID: 30287277.

77. Del Bene G, Calabro F, Giannerelli D, Plimack ER, Harshman LC, Yu EY, Crabb SJ, Pal SK, Alva AS, Powles T, De Giorgi U, Agarwal N, Bamias A, Ladoire S, Necchi A, Vaishampayan UN, Niegisch

G, Bellmunt J, Baniel J, Galsky MD, Sternberg CN. Neoadjuvant vs. adjuvant chemotherapy in muscle invasive bladder cancer: Analysis from the RISC database. *Front Oncol* 2018; 8:463. Epub November 19, 2018. PMID: 30510914. PMCID: 6252384.

78. Ramos JD, Holt SK, Schade GR, Galsky MD, Wright JL, Gore JL, Yu EY. Chemotherapy regimen is associated with venous thromboembolism risk in urothelial tract cancer patients. *BJU Int* 2019; 124(2):290-296. Epub January 22, 2019. PMID: 30667142. PMCID: 6641999. NIHMSID: 1007675.

79. Chu AT, Holt SK, Wright JL, Grivas P, Yu EY, Gore JL. Delays in radical cystectomy for patients with muscle-invasive bladder cancer. *Cancer* 2019; 125(12):2011-2017. Epub March 6, 2019. PMID: 30840335.

80. Schweizer MT, Gulati R, Beightol M, Konnick EQ, Cheng HH, de Sarkar N, Yu EY, Montgomery RB, Nelson PS, Pritchard CC. Clinical determinants for successful circulating tumor DNA analysis in prostate cancer. *Prostate* 2019; 79(7):701-708. Epub March 13, 2019. PMID: 30865311. PMCID: 6589085. NIHMSID: 1035778.

81. Bamias A, Tzannis K, Bamia C, Harshman LC, Crabb S, Wong YN, Pal S, De Giorgi U, Ladoire S, Theodore C, Agarwal N, Yu EY, Niegisch G, Sternberg C, Srinivas S, Vaishampayan U, Necchi A, Liontos M, Rosenberg J, Powles T, Bellmunt J, Galsky MD, RISC Investigators. The impact of cisplatin or non-cisplatin containing chemotherapy on long-term and conditional survival of patients with advanced urinary tract cancer. *Oncologist* 2019; 24(10):1348-1355. Epub April 1, 2019. PMID: 30936379. PMCID: 6795165.

82. Schweizer MT, Antonarakis ES, Bismar TA, Guedes LB, Cheng HH, Tretiakova MS, Vakar-Lopez F, Klemfuss N, Konnick EQ, Mostaghel EA, Hsieh AC, Nelson PS, Yu EY, Montgomery RB, True LD, Epstein JI, Lotan TL, Pritchard CC. Genomic characterization of prostatic ductal adenocarcinoma identifies a high prevalence of DNA repair gene mutations. *JCO Precis Oncol* 2019; 3:PO.18.00327. Epub April 18, 2019. PMID: 31123724. PMCID: 6528668. NIHMSID: 1025864.

83. Winters BR, De Sarkar N, Arora S, Bolouri H, Jana S, Vakar-Lopez Fm, Cheng HH, Schweizer MT, Yu EY, Grivas P, Lee JK, Kollath L, Holt SK, McFerrin L, Ha G, Nelson PS, Montgomery RB, Wright JL, Lam HM, Hsieh AC. Genomic dinstinctions between metastatic lower and upper tract urothelial carcinoma revealed through rapid autopsy. *JCI Insight* 2019; 5(13):e128728. Epub May 30, 2019. PMID: 31145100. PMCID: 6629128.

84. Martini A, Jia R, Ferket B, Plimack ER, Crabb SJ, Harshman LC, Yu EY, Powles T, Rosenberg JE, Pal SK, Vaishampayan UN, Necchi A, Wiklund NP, Mehrazin R, Waingankar N, Mazumdar M, Sfakianos JP, Galsky MD. Tumor downstaging as an intermediate endpoint to assess the activity of neoadjuvant systemic therapy in patients with muscle-invasive bladder cancer. *Cancer* 2019; 125(18):3155-3163. Epub May 31, 2019. PMID: 31150110. PMCID: 6859003.

85. Bandini M, Briganti A, Plimack ER, Niegisch G, Yu EY, Bamias A, Agarwal N, Sridhar SS, Sternberg CN, Vaishampayan U, Theodore C, Rosenberg JE, Bellmunt J, Galsky MD, Montorsi F, Necchi A. Modeling 1-year relapse-free survival after neoadjuvant chemotherapy and radical cystectomy in patients with clinical T2-4N0M0 urothelial bladder carcinoma: Endpoints for phase 2 trials. *Eur Urol Oncol* 2019; 2(3):248-256. Epub September 7, 2018. PMID: 31200838. PMCID: 7552889.

86. Pederzoli F, Bandini M, Briganti A, Plimack ER, Niegisch G, Yu EY, Bamias Am Agarwal N, Sridhar SS, Sternberg CN, Vaishampayan UN, Theodore C, Rosenberg JE, Bellmunt J, Galsky MD, Gallina A, Salonia A, Montorsi F, Necchi A, RISC Investigators. Incremental utility of adjuvant chemotherapy in muscle invasive bladder cancer: Quantifying the relapse risk associated with therapeutic effect. *Eur Urol* 2019; 76(4):425-429. Epub July 11, 2019. PMID: 31303258. PMCID: 6852645.

87. Moschini M, Xylinas E, Zamboni S, Mattei A, Niegisch G, Yu EY, Bamias A, Agarwal N, Sridhar SS, Sternberg CN, Vaishampayan UN, Rosenberg JE, Bellmunt J, Galsky MD, Montorsi F, Necchi A, RISC Investigators. Efficacy of surgery in the primary tumor site for metastatic urothelial cancer: Analysis of an international, multicenter, multidisciplinary database. *Eur Urol Oncol* 2019; 3(1):94-101. Epub July 12, 2019. PMID: 31307962. PMCID: 6954983.

88. Rosenberg JE, O'Donnell PH, Balar AV, McGregor BA, Heath EI, Yu EY, Galsky MD, Hahn NM, Gartner EM, Pinelli JM, Liang SY, Melhem-Bertrandt A, Petrylak DP. Pivotal trial of enfortumab vedotin in urothelial carcinoma after platinum and anti-programmed death 1/programmed death ligand 1 therapy. *J Clin Oncol* 2019; 37(29):2592-2600. Epub July 29, 2019. PMID: 31356140. PMCID: 6784850.

89. Labrecque MP, Coleman IM, Brown LG, True LD, Kollath L, Lakely B, Nguyen HM, Yang YC, Gil da Costa RM, Kaipainen A, Coleman R, Higano CS, Yu EY, Cheng HH, Mostaghel EA, Montgomery B, Schweizer MT, Hsieh AC, Lin DW, Corey E, Nelson PS, Morrissey C. Molecular profiling stratifies diverse phenotypes of treatment-refractory metastatic castration-resistant prostate cancer. *J Clin Invest* 2019; 130:4492-4505. Epub July 30, 2019. PMID: 31361600. PMCID: 6763249.

90. Beltran H, Hruszkewycz A, Scher H, Hildesheim J, Isaacs J, Yu EY, Kelly K, Lin D, Dicker A, Arnold J, Hecht T, Wicha M, Sears R, Rowley D, White R, Gulley J, Lee J, Diaz-Meco M, Small E, Shen M, Knudsen K, Goodrich D, Lotan T, Zoubeidi A, Sawyers C, Rudin C, Loda M, Thompson T, Rubin M, Tawab-Amiri A, Dahut W, Nelson P. The role of lineage plasticity in prostate cancer therapy resistance. *Clin Cancer Res* 2019; 25(23):6916-6924. Epub July 30, 2019. PMID: 31363002. PMCID: 6891154.

91. Martinez Chanza N, Werner L, Plimack E, Yu EY, Alva AS, Crabb SJ, Powles T, Rosenberg JE, Baniel J, Vaishampayan UN, Berthold DR, Ladoire S, Hussain SA, Milowsky MI, Agarwal N, Necchi A, Pal SK, Sternberg CN, Bellmunt J, Galsky MD, Harshman LC; RISC Investigators. Incidence, patterns and outcomes with adjuvant chemotherapy for residual disease after neoadjuvant chemotherapy in muscle-invasive urinary tract cancers. *Eur Urol Oncol* 2019; 3(5):671-679. Epub January 30, 2019. PMID: 31411990. PMCID: 8449851.

92. Black AJ, Zargar H, Zargar-Shoshtari K, Fairey AS, Mertens LS, Dinney CP, Mir MC, Krabbe LM, Cookson MS, Jacobsen NE, Griffin J, Montgomery JS, Vasdev N, Yu EY, Xylinas E, Campain NJ, Kassouf W, Dall'Era MA, Seah JA, Ercole CE, Horenblas S, McGrath JS, Aning J, Shariat SF, Wright JL, Thorpe AC, Morgan TM, Holzbeierlein JM, Bivalacqua TJ, North S, Barocas DA, Lotan Y, Grivas P, Stephensen AJ, Shah JB, van Rhijn BW, Spiess PE, Daneshmand S, Sridhar SS, Black PC. The prognostic value of the neutrophil-to-lymphocyte ratio in patients with muscle-invasive bladder cancer treated with neoadjuvant chemotherapy and radical cystectomy. *Urol Oncol* 2020; 38(1):3.e17-3.e27. Epub October 29, 2019. PMID: 31676278.

93. Petrylak DP, De Wit R, Chi KN, Drakaki A, Sternberg CN, Nishiyama H, Guana DC, Hussain SA, Flechon A, Bamias A, Yu EY, van der Heijden MS, Matsubara N, Alekseev B, Necchi A, Geczi L, Ou YC, Coskun HS, Su WP, Bedke J, Gakis G, Percent IJ, Lee JL, Tucci M, Semenov A, Laestadius F, Peer A, Tortora G, Safina S, Garcia del Muro X, Rodriguez-Vida A, Cicin I, Harputluoglu H, Tagawa S, Vaishampayan U, Aragon-Ching J, Hamid O, Liepa AM, Wijayawardana S, Russo F, Walgren RA, Zimmermann AH, Hozak R, Bell-McGuinn KM, Powles, for the RANGE study investigators. Overall survival and updated results of the randomized phase 3 RANGE trial: ramucirumab/docetaxel versus placebo/docetaxel in platinum-refractory, advanced urothelial carcinoma. *Lancet Oncol* 2019; 21(1):105-120. Epub November 18, 2019. PMID: 31753727. PMCID: 6946880.

94. Caffo O, Wissing M, Bianchini D, Bergman A, Thomsen FB, Schmid S, Yu EY, Bournakis E, Sella A, Zagonel V, De Giorgi U, Tucci M, Gelderblom H, Galli L, Pappagallo G, Bria E, Sperduti I, Oudard S; CASTOR study investigators. Survival outcomes from a cumulative analysis of worldwide observational studies on sequential use of new agents in metastatic castration-resistant prostate cancer. *Clin Genitourin Cancer* 2019; 18(1):68-76. Epub September 27, 2019. PMID: 31767448.

95. Bamias A, Tzannis K, Harshman LC, Crabb SJ, Wong YN, Pal SK, De Giorgi U, Ladoire S, Agarwal N, Yu EY, Niegisch G, Necchi A, Sternberg CN, Srinivas S, Alva A, Vaishampayan U, Cerbone L, Liontos M, Rosenberg J, Powles T, Bellmunt J, Galsky MD. Impact of contemporary patterns of chemotherapy utilization on survival in patients with advanced cancer of the urinary tract: a Retrospective International Study of Invasive/Advanced Cancer of the Uorthelium (RISC). *Ann Oncol* 2019; 30(11):1841. Epub November 1, 2019. PMID: 31868903. PMCID: 8902985.

96. Diamantopoulos LN, Khaki AR, Sonpavde G, Venur VA, Yu EY, Wright JL, Grivas P. Central nervous system metastasis in patients with urothelial carcinoma: institutional experience and a comprehensive review of the literature. *Clin Genitourin Cancer* 2020; 18(3):e266-e276. Epub December 5, 2019. PMID: 32178979. PMCID: 7272305.

97. Khaki AR, Li A, Diamantopoulos LN, Bilen M, Santos V, Esther J, Morales R, Devitt M, Nelson A, Hoimes C, Shreck E, Hussein A, Gartrell B, Sankin A, Rodriguez-Vida A, Lythgoe M, Pinato D, Drakaki A, Joshi M, Velho PI, Hahn N, Liu S, Buznego LA, Duran I, Moses M, Jain J, Murgic J, Baratam P, Barata P, Tripathi A, Zakharia Y, Galsky M, Sonpavde G, Yu EY, Shankaran V, Lyman GH, Grivas P. Impact of performance status on treatment outcomes: A real-world study of advanced urothelial cancer treated with checkpoint inhibitors. *Cancer* 2019; 126(6):1208-1216. Epub December 12, 2019. PMID: 31829450. PMCID: 7050422.

98. Diamantopoulos LN, Winters BR, Grivas P, Ngo SD, Zeng J, Hsieh AC, Gore JL, Liao JJ, Yu EY, Schade GR, Psutka SP, Schweizer MT, Lee JH, Dighe M, Lin DW, Cheng HH, Daya JM, Tretiakova MS, True LD, Russell KJ, Vakar-Lopez F, Montgomery RB. Bladder Cancer Multidisciplinary Clinic model influences disease assessment and impacts treatment recommendations. *Bladder Cancer* 2019; 5(4):289-298. Epub December 30, 2019.

99. Miller NJ, Khaki AR, Diamantopoulos LN, Bilen MA, Santos V, Agarwal N, Morales-Barrera R, Devitt M, Nelson A, Hoimes CJ, Shreck E, Assi H, Gartrell BA, Sankin A, Rodriguez-Vida A, Lythgoe M, Pinato DJ, Drakaki A, Joshi M, Velho PI, Hahn N, Liu S, Buznego LA, Duran I, Moses M, Jain J, Murgic J, Barata P, Tripathi A, Zakharia Y, Galsky MD, Sonpavde G, Yu EY, Lyman GH, Grivas P. Histologic Subtypes and Response to PD-1/PD-L1 Blockade in Advanced Urothelial

Cancer: A Retrospective Study. *J Urol* 2020; 204(1):63-70. Epub January 23, 2020. PMID: 31971495. PMCID: 7289665.

100. Bandini M, Pederzoli F, Madison R, Briganti A, Ross JS, Niegisch G, Yu EY, Bamias A, Agarwal N, Sridhar SS, Rosenberg JE, Bellmunt J, Pal SK, Galsky MD, Luciano R, Gallina A, Salonia A, Montorsi F, Ali SM, Chung JH, Necchi A. Unfavorable cancer-specific survival after neoadjuvant chemotherapy and radical cystectomy in patients with bladder cancer and squamous cell variant: A multi-institutional study. *Clin Genitourin Cancer* 2020; 18(5):e543-e556. Epub February 8, 2020. PMID: 32144050. PMCID: 8491463.

101. D'Andrea D, Black PC, Zargar H, Zargar-Shoshtari K, Zehetmayer S, Fairey AS, Mertens LS, Dinney CP, Mir MC, Krabbe LM, Cookson MS, Jacobsen NE, Montgomery JS, Vasdev N, Yu EY, Xylinas E, Campain NJ, Kassouf W, Dall'Era, MA, Seah J, Ercole CE, Horenblas S, Sridhar SS, McGrath JS, Aning J, Wright JL, Thorpe AC, Morgan TM, Holzbeierlein JM, Bivalacqua TJ, North S, Barocas DA, Lotan Y, Grivas P, Stephenson AJ, Shah JB, Van Rhijn BW, Daneshmand S, Spiess PE, Shariat SF. Impact of sex on response to neoadjuvant chemotherapy in patients with bladder cancer. *Urol Oncol* 2020; 38(7):639.e1-639.e9. Epub February 11, 2020. PMID: 32057595.

102. Wong RL, Duong MT, Tangen CM, Agarwal N, Cheng HH, Vogelzang NJ, Hussain M, Thompson IM Jr., Quinn DI, Yu EY. Survival outcomes and risk group validation from SWOG S0925, a randomized phase II study of cixutumumab in new metastatic hormone-sensitive prostate cancer. *Prostate Cancer Prostatic Dis* 2020; 23(3):486-493. Epub February 13, 2020. PMID: 32055002. PMCID: 7423720.

103. Madan RA, Antonarakis ES, Drake CG, Fong L, Yu EY, McNell DG, Lin DW, Chang NN, Sheikh NA, Gulley JL. Putting the pieces together: Completing the mechanism of action jigsaw for Sipuleucel-T. *J Natl Cancer Inst* 2020; 112(6):562-573. Epub March 7, 2020. PMID: 32145020. PMCID: 7301097.

104. Yu EY, Hancock ML, Aronson W, Flaig T, Belkoff L, Tutrone R, Taylor R, Hardigan PC, Getzenberg RH. Phase 2 trial of GTx-758, and estrogen receptor alpha agonist, in men with castration-resistant prostate cancer. *Clin Genitourin Cancer* 2020; 18(6):436-443. Epub March 27, 2020. PMID: 32321673.

105. Diamantopoulos LN, Khaki AR, Grivas P, Gore JL, Schade GR, Hsieh AC, Lee JK, Yezefski T, Yu EY, Schweizer MT, Cheng HH, Psutka SP, Lin DW, Tretiakova MS, Vakar-Lopez F, Montgomery RB, Wright JL. Plasmacytoid urothelial carcinoma: Response to chemotherapy and oncologic outcomes. *Bladder Cancer* 2020; 6(1):71-81. Epub March 28, 2020. PMID: 34109262. PMCID: 8186525.

106. Graham LS, Montgomery B, Cheng HH, Yu EY, Nelson P, Pritchard C, Alva A, Schweizer MT. Mismatch repair deficiency in metastatic prostate cancer: Response to PD-1 blockade and standard therapies. *PLoS One* 2020; 15(5):e0233260. Epub May 26, 2020. PMID: 32453797. PMCID: 7301097. PMCID: 7250457.

107. Giri VN, Knudsen KE, Kelly WK, Cheng HH, Cooney KA, Cookson MS, Dahut W, Weissman S, Soule HR, Petrylak DP, Dicker AP, AlDubayan SH, Toland AE, Pritchard CC, Pettaway CA, Daly MB, Mohler JL, Parsons JK, Carroll PR, Pilarski R, Blanco A, Woodson A, Rahm A, Taplin ME, Polascik TJ, Helfand BT, Hyatt C, Morgans AK, Feng F, Mullane M, Powers J, Concepcion R, Lin

DW, Wender R, Mark JR, Costello A, Burnett AL, Sartor O, Isaacs WB, Xu J, Weitzel J, Andriole GL, Beltran H, Briganti A, Byrne L, Calvaresi A, Chandrasekar T, Chen DYT, Den RB, Dobi A, Crawford ED, Eastham J, Eggener S, Freedman ML, Garnick M, Gomella PT, Handley N, Hurwitz MD, Izes J, Karnes RJ, Lallas C, Languino L, Loeb S, Lopez AM, Loughlin KR, Lu-Yao G, Malkowicz SB, Mann M, Mille P, Miner MM, Morgan T, Moreno J, Mucci L, Myers RE, Nielsen SM, O'Neil B, Pinover W, Pinto P, Poage W, Raj GV, Rebbeck TR, Ryan C, Sandler H, Schiewer M, Scott EMD, Szymaniak B, Tester W, Trabulsi EJ, Vapiwala N, Yu EY, Zeigler-Johnson C, Gomella LG. Implementation of Germline Testing for Prostate Cancer: Philadelphia Prostate Cancer Consensus Conference 2019. *J Clin Oncol* 2020; 38(24):2798-2811. Epub June 9, 2020. PMID: 32516092. PMCID: 7430215.

108. [á]Grunewald CM, [á]Henn A, Galsky MD, Plimack ER, Harshman LC, Yu EY, Crabb SJ, Pal SK, Alva AS, Powles T, De Giorgi U, Agarwal N, Bamias A, Ladoire S, Necchi A, Vaishampayan UN, Sternberg CN, Bellmunt J, Baniel J, Niegisch G. Impact of timing of adjuvant chemotherapy following radical cystectomy for bladder cancer on patient survival. *Urol Oncol* 2020; 38(12):934.e1-934.e9. Epub July 10, 2020. PMID: 32660788. [á]*These authors contributed equally to this work.*

109. Mir MC, Marchioni M, Zargar H, Zargar-Shoshtari K, Fairey AS, Mertens LS, Dinney CP, Krabbe LM, Cookson MS, Jacobsen NE, Griffin J, Montgomery JS, Vasdev N, Yu EY, Xylinas E, McGrath JS, Kassouf W, Dall'Era MA, Sridhar SS, Aning J, Shariat SF, Wright JL, Thorpe AC, Morgan TM, Holzbeierlein JM, Bivalacqua TJ, North S, Barocas DA, Lotan Y, Grivas P, Stephenson AJ, Shah JB, van Rhijn BW, Spiess PE, Daneshmand D, Black PC. Nomogram predicting bladder cancer specific mortality after neoadjuvant chemotherapy and radical cystectomy for muscle-invasive bladder cancer: Results of an international consortium. *Eur Urol Focus* 2021; 7(6):1347-1354. Epub August 6, 2020. PMID: 32771446.

110. Sokolova AO, Shirts BH, Konnick EQ, Tsai GJ, Goulart BHL, Montgomery B, Pritchard CC, Yu EY, Cheng HH. Complexities of next-generation sequencing in solid tumors: Case studies. *J Natl Compr Canc Netw* 2020; 18(9):1150-1155. PMID: 32886903.

111. Carlson AS, Acevedo RI, Lim D, Gulati R, Gawne A, Sokolova AO, Cheng HH, Nelson PS, Montgomery B, Yu EY, Schweizer MT. Impact of mutations in homologous recombination repair genes on treatment outcomes for metastatic castration resistant prostate cancer. *PLoS One* 2020; 15(9):e0239686. Epub September 30, 2020. PMID: 32997692. PMCID: 7526881.

112. Crawford ED, Andriole G, Freedland SJ, Garnick M, Gomella LG, Henderson J, Higano C, Kader AK, Kane C, Keane TE, Koo PJ, Petrylak DP, Reiter RE, Slovin SF, Yu EY. Evolving understanding and categorization of prostate cancer: preventing progression to metastatic castration-resistant prostate cancer: RADAR IV. *Can J Urol* 2020; 27(5):10352-10362. PMID: 33049187.

113. Jensen K, Konnick EQ, Schweizer M, Sokolova A, Grivas P, Cheng HH, Klemfuss N, Beightol M, Yu EY, Nelson PS, Montgomery B, Pritchard CC. Association of clonal hematopoiesis in DNA repair genes with prostate cancer plasma cell-free DNA testing interference. *JAMA Oncol* 2021; 7(1):107-110. Epub November 5, 2020. PMID: 33151258. PMCID: 7645740.

114. Soria F, Black PC, Fairey AS, Cookson MS, Yu EY, Kassouf W, Dall'Era MA, Sridhar SS, McGrath JS, Wright JL, Thorpe AC, Morgan TM, Daneshmand S, Holzbeierlein JM, Bivalacqua TJ, North S, Barocas DA, Lotan Y, Grivas P, Stephenson AJ, Shah JB, van Rhijn BW, Spiess PE, Shariat SF, Gontero P. Neoadjuvant chemotherapy plus radical cystectomy versus radical cystectomy

alone in clinical T2 bladder cancer without hydronephrosis. *BJU Int* 2020; 128(1):79-87. Epub November 5, 2020. PMID: 33152179.

115. Diamantopoulos LN, Holt SK, Khaki AR, Sekar RR, Gadzinski AJ, Nyame YA, Vakar-Lopez F, Tretiakova MS, Psutka SP, Gore JL, Lin DW, Schade GR, Hsieh AC, Lee JK, Yezefski T, Schweizer MT, Cheng HH, Yu EY, True LD, Montgomery RB, Grivas P, Wright JL. Response to neoadjuvant chemotherapy and survival in micropapillary urothelial carcinoma: data from a tertiary referral center and Surveillance, Epidemiology and End Results (SEER) program. *Clin Genitourin Cancer* 2020; 19(2):144-54. Epub October 14, 2020. PMID: 33160889. PMCID: 8044249.

116. Do OA, Ferris LA, Holt SK, Ramos JD, Harshman LC, Plimack ER, Crabb SJ, Pal SK, De Giorgi U, Ladoire S, Baniel J, Necchi A, Vaishampayan UN, Bamias A, Bellmunt J, Srinivas S, Dorff TB, Galsky MD, Yu EY. Treatment of metastatic urothelial carcinoma after previous cisplatin-based chemotherapy for localized disease: A retrospective comparison of different chemotherapy regimens. *Clin Genitourin Cancer* 2020; 19(2):125-34. Epub November 12, 2020. PMID: 33309564.

117. Nyame YA, Holt SK, Diamontopolous L, Winters BR, Psutka SP, Dash A, Schade GR, Lin DW, Yu EY, Grivas P, Gore JL, Wright JL. Social and clinical correlates of neoadjuvant chemotherapy in Medicare beneficiaries with muscle invasive bladder cancer from 2004-2015. *Urology* 2021; 149:154-160. Epub December 26, 2020. PMID: 33373709.

118. Khaki AR, Li A, Diamantopoulos LN, Miller NJ, Carril-Ajuria L, Castellano D, De Kouchkovsky I, Koshkin V, Park J, Alva A, Bilen MA, Stewart T, Santos V, Agarwal N, Jain J, Zakharia Y, Morales-Barrera R, Devitt M, Nelson A, Hoimes CJ, Shreck E, Gartrell BA, Sankin A, Tripathi A, Zakopoulou R, Bamias A, Rodriguez-Vida A, Drakaki A, Liu S, Kumar V, Lythgoe MP, Pinato DJ, Murgic J, Frobe A, Joshhi M, Velho PI, Hahn N, Buznego LA, Duran I, Moses M, Barata P, Galsky MD, Sonpavde G, Yu EY, Shankaran V, Lyman GH, Grivas P. A new prognostic model in patients with advanced urothelial carcinoma treated with first-line immune checkpoint inhibitors. *Eur Urol Oncol* 2021; 4(3):464-72. Epub January 7, 2021. PMID: 33423945. PMCID: 8169524.

119. Diamantopoulos LN, Sekar RR, Holt SK, Khaki AR, Miller NJ, Gadzinski A, Nyame YA, Vakar-Lopez F, Tretiakova MS, Psutka SP, Gore JL, Lin DW, Schade GR, Hsieh AC, Lee JK, Yezefski T, Schweizer MT, Cheng HH, Yu EY, True LD, Montgomery RB, Grivas P, Wright JL. Patterns and timing of perioperative blood transfusion and association with outcomes after radical cystectomy. *Urol Oncol* 2021; 39(8):496.e1-496.e8. Epub February 4, 2021. PMID: 33551249.

120. Esagian SM, Khaki AR, Diamantopoulos LN, Carril-Ajuria L, Castellano D, De Kouchkovsky I, Park JJ, Alva A, Bilen MA, Stewart TF, McKay RR, Santos VS, Agarwal N, Jain J, Zakharia Y, Morales-Barrera R, Devitt ME, Nelson A, Hoimes CJ, Shreck E, Gartrell BA, Sankin A, Tripathi A, Zakopoulou R, Bamias A, Rodriguez-Vida A, Drakaki A, Liu S, Kumar V, Lythgoe MP, Pinato DJ, Murgic J, Frobe A, Joshi M, Issacsson Velho P, Hahn N, Alonso Buznego L, Duran I, Moses M, Barata P, Galsky MD, Sonpavde G, Yu EY, Msaouel P, Koshkin VS, Grivas P. Immune checkpoint inhibitors in advanced upper and lower tract urothelial carcinoma: a comparison of outcomes. *BJU Int* 2021; 128(2):196-205. Epub February 8, 2021. PMID: 33556233.

121. Guo C, Crespo M, Gurel B, Dolling D, Rekowski J, Sharp A, Petremolo A, Sumanasuriya S, Rodrigues DN, Ferreira A, Pereira R, Figgueiredo I, Mehra N, Lambros MBK, Neeb A, Gil V, Seed G, Terstappen L, Alimonti A, Drake CG, Yuan W, de Bono JS; International SU2C PCF Prostate

Cancer Dream Team (Robinson D, Van Allen EM, Wu YM, Schultz N, Lonigro RJ, Mosquera JM, Montgomery B, Taplin ME, Pritchard CC, Attard G, Beltran H, Abida W, Bradley RK, Vinson J, Cao X, Vats P, Kunju LP, Hussain M, Tomlins SA, Cooney KA, Smith DC, Brennan C, Siddiqui J, Mehra R, Chen Y, Rathkopf DE, Morris MJ, Solomon SB, Durack JC, Reuter VE, Gopalan A, Gao J, Loda M, Lis RT, Bowden M, Balk SP, Gaviola G, Sougnez C, Gupta M, Yu EY, Mostaghel EA, Cheng HH, Mulcahy H, True LD, Plymate SR, Dvinge H, Ferraldeschi R, Flohr P, Miranda S, Zafeiriou Z, Tunariu N, Mateo J, Perez-Lopez R, Demichelis F, Robinson BD, Schiffman M, Nanus DM, Tagawa ST, Sigaras A, Eng KW, Elemento O, Sboner A, Heath EI, Scher HI, Pienta KJ, Kantoff P, de Bono JS, Rubin MA, Nelson PS, Garraway LA, Sawyers CL, Chinnaiyan AM). CD38 in advanced prostate cancers. *Eur Urol* 2021; 79(6):736-746. Epub March 1, 2021. PMID: 33678520. PMCID: 8175332.

122. Graham LS, Reder N, Gulati R, Schade G, Wright J, Grivas P, Yezefski T, Nega K, Alexander K, Hou W, Yu EY, Montgomery B, Mostaghel E, Ellis W, True L, Lin DW, Nelson PS, Schweizer MT. Targeting backdoor androgen synthesis through AKR1C3 inhibition: A presurgical hormonal ablative neoadjuvant trial in high risk localized prostate cancer. *Prostate* 2021; 81(7):418-426. Epub March 23, 2021. PMID: 33755225. PMCID: 8044035.

123. McKay R, Kwak L, Crowdis J, Sperger J, Zhao S, Xie W, Werner L, Lis R, Zhang Z, Wei X, Lang J, Van Allen E, Bhatt R, Yu EY, Nelson PS, Bubley G, Montgomery B, Taplin ME. Phase 2 multicenter study of enzalutamide in metastatic castration resistant prostate cancer to identify mechanisms driving resistance. *Clin Cancer Res* 2021; 27(13):3610-19. Epub April 13, 2021. PMID: 33849963. PMCID: 8254786.

124. Muzi M, O'Sullivan FS, Perk TG, Muzi JP, Mankoff DA, Jeraj R, Duan F, Yu EY. Whole-body ^{18}F-Fluoride PET SUV imaging to monitor response to dasatinib therapy in castration-resistant prostate cancer bone metastases: Secondary results from ACRIN 6687. *Tomography* 2021; 7(2):139-153. Epub April 25, 2021. PMID: 33923126. PMCID: 8167705.

125. Yu EY, Petrylak DP, O'Donnell PH, Lee JL, van der Heijden MS, Loriot Y, Stein MN, Necchi A, Kojima T, Harrison MR, Park SH, Quinn DI, Heath EI, Rosenberg JE, Steinberg J, Liang SY, Trowbridge J, Campbell M, McGregor B, Balar AV. Pivotal single-arm phase 2 trial of enfortumab vedotin after PD-1/PD-L1 inhibitors in cisplatin-ineligible patients with advanced urothelial carcinoma. *Lancet Oncol* 2021; 22(6):872-882. Epub May 12, 2021. PMID: 33991512.

126. Powles T, Csoszi T, Ozguroglu M, Matsubara N, Geczi L, Cheng SYS, Fradet Y, Oudard S, Vulsteke C, Barrera RM, Flechon A, Gunduz S, Loriot Y, Rodriguez-Vida A, Mamtani R, Yu EY, Nam K, Imai K, Moreno BH, Alva A for the KEYNOTE-361 Investigators. Pembrolizumab alone or combined with chemotherapy versus chemotherapy as first-line therapy for advanced urothelial carcinoma (KEYNOTE-361): a randomized, open-label, phase 3 study. *Lancet Oncol* 2021; 22(7):931-945. Epub May 26, 2021. PMID: 34051178.

127. Schweizer MT, Sivakumar S, Tukachinsky H, Coleman I, De Sarkar N, Yu EY, Konnick EQ, Nelson PS, Pritchard CC, Montgomery B. Concordance of DNA repair gene mutations in paired primary prostate cancer samples and metastatic tissue or cell-free DNA. *JAMA Oncol* 2021; 7(9):1-5. Epub June 4, 2021. PMID: 34086042. PMCID: 8446811.

127. Wong RL, Ferris LA, Do OA, Holt SK, Ramos JD, Crabb SJ, Sternberg CN, Bellmunt J, Ladoire S, De Giorgi U, Harshman LC, Vaishampayan UN, Necchi A, Srinivas S, Pal SK, Niegisch G, Dorff TB,

Galsky MD, Yu EY. Efficacy of platinum rechallenge in metastatic urothelial carcinoma after previous platinum-based chemotherapy for metastatic disease. *Oncologist* 2021; 26(12):1026-1034. Epub August 6, 2021. PMID: 34355457. PMCID: 8649023.

128. D'Andrea D, Black PC, Zargar H, Zargar-Shoshtari K, Soria F, Fairey AS, Mertens LS, Dinney CP, Mir MC, Krabbe LM, Cookson MS, Jacobsen NE, Montgomery JS, Vasdev N, Yu EY, Xylinas E, Campain NJ, Kassouf W, Dall'Era MA, Seah JA, Ercole CE, Horenblas S, Sridhar SS, McGrath JS, Aning J, Wright JL, Thorpe AC, Morgan TM, Holzbeierlein JM, Bivalacqua TJ, North S, Barocas DA, Lotan Y, Grivas P, Stephenson AJ, Shah JB, van Rhijn BW, Daneshmand S, Spiess PE, Shariat SF. Association of age with response to preoperative chemotherapy in patients with muscle-invasive bladder cancer. *World J Urol* 2021; 39(12):4345-4354. Epub August 9, 2021. PMID: 34370078. PMCID: 8602146.

129. Mostaghel E, Marck B, Kolokythas O, Chew F, Yu EY, Schweizer M, Cheng H, Balk S, Kantoff P, Taplin ME, Sharifi N, Matsumoto A, Nelson P, Montgomery B. Circulating and intra-tumoral adrenal androgens correlate with response to abiraterone in men with castration resistant prostate cancer. *Clin Cancer Res* 2021; 27(21):6001-6011. Epub August 18, 2021. PMID: 34407973. PMCID: 8563401.

130. D'Andrea D, Black PC, Zargar H, Dinney CP, Soria F, Cookson MS, Montgomery JS, Kassouf W, Dall'Era MA, Sridhar SS, McGrath JS, Wright JL, Thorpe AC, Holzbeierlein JM, Carrion DM, Di Trapani E, Bivalacqua TJ, North S, Barocas DA, Lotan Y, Grivas P, Stephenson AJ, van Rhijn BW, Daneshmand S, Spiess PE, Shariat SF, Zargar-Shoshtar K, Mertens LS, Fairey AS, Mir MC, Krabbe LM, Jacobsen NE, Vasdev N, Yu EY, Xylinas E, Pradere B, Pichler R, Campain NJ, Seah JA, Ercole CE, Horenblas S, Aning J, Morgan TM, Shah JB, Moschini M. Identifying the optimal number of neoadjuvant chemotherapy cycles in patients with muscle-invasive bladder cancer. *J Urol* 2021; 39(12):4345-4354. Epub August 9, 2021. PMID: 34445891.

131. Pachynski R, Morishima C, Szmulewitz R, Harshman LC, Appleman LJ, Monk JP, Bitting RL, Kucuk O, Millard F, Seigne JD, Fling SP, Maecker H, Duault C, Ramchurren N, Hess B, D'Amico L, Lacroix A, Kaiser JC, Morre M, Gregoire A, Cheever MA, Yu EY, Fong L. IL-7 expands lymphocyte populations and enhances immune responses to sipuleucel-T in patients with metastatic castrate-resistant prostate cancer. *J Immunother Cancer* 2021; 9(8):e002903. Epub August 2021. PMID: 34452927. PMCID: 8404457.

132. Chang E, Apolo AB, Bangs R, Chisolm S, Duddalwar, Efstathiou JA, Goldberg KB, Hansel DE, Kamat AM, Kluetz PG, Lerner SP, Plimack E, Prowell T, Singh H, Suzman D, Yu EY, Zhang H, Beaver JA, Pazdur R, Weinstock C, Galsky MD. Opportunities to refine neoadjuvant therapy clinical trial design for muscle-invasive bladder cancer prior to cystectomy: report from a joint United States FDA/BCAN workshop. *Nat Rev Urol* 2021; 19(1):37-46. Epub September 10, 2021. PMID: 34508246.

133. Sokolova AO, Marshall CH, Lozano R, Gulati R, Ledet EM, De Sarkar N, Grivas P, Higano CS, Montgomery B, Nelson PS, Olmos D, Sokolov V, Schweizer MT, Yezefski TA, Yu EY, Paller CJ, Sartor O, Castro E, Antonarakis ES, Cheng HH. Efficacy of systemic therapies in men with metastatic castration resistant prostate cancer harboring germline ATM versus BRCA2 mutations. *Prostate* 2021; 81(16):1382-1389. Epub September 13, 2021. PMID: 34516663. PMCID: 8563438.

134. Makrakis D, Talukder R, Diamantopoulos LN, Carril-Ajuria L, Castellano D, De Kouchkovsky I, Koshkin VS, Park JJ, Alva A, Bilen MA, Stewart TF, McKay RR, Santos VS, Agarwal N, Jain J, Zakharia Y, Morales-Barrera R, Devitt ME, Grant M, Lythgoe MP, Pinato DJ, Nelson A, Hoimes CJ, Shreck E, Gartrell BA, Sankin A, Tripathi A, Zakopoulou R, Bamias A, Murgic J, Frobe A, Rodriguez-Vida A, Drakaki A, Liu S, Kumar V, Di Lorenzo G, Joshi M, Isaacsson-Velho P, Buznego LA, Duran I, Moses M, Barata P, Sonpavde G, Yu EY, Wright JL, Grivas P, Khaki AR. Association of prior local therapy and outcomes with PD(L)1 inhibitor in advanced urothelial cancer. *BJU Int* 2021; Epub October 1, 2021. PMID: 34597472.

135. Schoder H, Hope TA, Knopp M, Kelly WK, Michalski JM, Lerner SP, Tawab-Amiri A, Mann BS, Lin DW, Yu EY, Chen RC, Beach GC, Reeves SA, Members of the Working Group, Shankar LK. Considerations on integrating Prostate-Specific Membrane Antigen positron emission tomography imaging into clinical prostate cancer trials by National Clinical Trials Network Cooperative Groups. *J Clin Oncol* 2022; 40(13):1500-1505. Epub January 11, 2022. PMID: 35015566.

136. de Wit R, Powles T, Castellano D, Necchi A, Lee JL, van der Heijden MS, Matsubara N, Bamias A, Flechon A, Sternberg CN, Drakaki A, Yu EY, Zimmermann AH, Long A, Walgren RA, Gao L, Bell-McGuinn KM, Petrylak DP. Exposure-response relationship of ramucirumab in RANGE, a randomized phase III trial in advanced urothelial carcinoma refractory to platinum therapy. *Br J Clin Pharmacol* 2022; 88(7):3182-3192. Epub January 13, 2022. PMID: 35029306. PMCID: 9302693.

137. Talukder R, Makrakis D, Diamantopoulos LN, Carril-Ajuria L, Castellano D, De Kouchkovsky I, Koshkin VS, Park JJ, Alva A, Bilen MA, Stewart TF, McKay RR, Santos VS, Agarwal N, Jain J, Zakharia Y, Morales-Barrera R, Devitt ME, Grant M, Lythgoe MP, Pinato DJ, Nelson A, Hoimes CJ, Shreck E, Gartrell BA, Sankin A, Tripathi A, Zakopoulou R, Bamias A, Murgic J, Frobe A, Rodriguez-Vida A, Drakaki A, Liu S, Kumar V, Di Lorenzo G, Joshi M, Velho PI, Buznego LA, Duran I, Moses M, Barata P, Sonpavde G, Yu EY, Wright JL, Grivas P, Khaki AR. Response and outcomes to immune checkpoint inhibitors in advanced urothelial cancer based on prior intravesical BCG. *Clin Genitourin Cancer* 2022; 20(2):165-175. Epub December 17, 2021. PMID: 35078711. PMCID: 8995351.

138. Smith MR, Scher HI, Sandhu S, Efstathiou E, Lara PN Jr, Yu EY, George DJ, Chi KN, Saad F, Sthl O, Olmos D, Danila DC, Mason GE, Espina BM, Zhao X, Urtishak KA, Francis P, Lopez-Gitlitz A, Fizazi K; GALAHAD investigators. Niraparib in patients with metastatic castration-resistant prostate cancer and DNA repair gene defects (GALAHAD): a multicentre, open-label, phase 2 trial. *Lancet Oncol* 2022; 23(3):362-373. Epub February 4, 2022. PMID: 35131040. PMCID: 9361481.

139. McGregor B, O'Donnell PH, Balar A, Petrylak D, Rosenberg J, Yu EY, Quinn DI, Heath EI, Campbell M, Hepp Z, McKay C, Steinberg J, Regnault A, Mazerolle F, Galsky MD. Health-related quality of life of patients with locally advanced or metastatic urothelial cancer treated with enfortumab vedotin after platinum and PD-1/PD-L1 inhibitor therapy: Results from Cohort 1 of the phase 2 EV-201 clinical trial. *Eur Urol* 2022; 81(5):515-522. Epub February 12, 2022. PMID: 35168844. PMCID: 9385268. NIHMSID: 1828733.

140. Greer MD, Schaub SK, Bowen SR, Liao JJ, Russell K, Chen JJ, Weg ES, Schade GR, Gore JL, Psutka SP, Montgomery RB, Schweizer M, Yu EY, Grivas P, Wright JL, Zeng J. A prospective study of a resorbable intravesical fiducial marker for bladder cancer radiation therapy. *Adv*

Radiat Oncol 2022; 7(2):100858. Epub November 21, 2021. PMID: 35387424. PMCID: 8977855.

141. Yu EY, Kolinsky M, Berry WR, Retz M, Mourey L, Piulats JM, Appleman LJ, Romano E, Gravis G, Gurney H, Bogemann M, Emmenegger U, Joshua AM, Linch M, Sridhar S, Conter HJ, Laguerre B, Massard C, Li XT, Schloss C, Poehlein CH, de Bono JS. Pembrolizumab plus docetaxel and prednisone in patients with metastatic castration-resistant prostate cancer: Long-term results from the phase 1b/2 KEYNOTE-365 Cohort B study. *Eur Urol* 2022; 82(1):22-30. Epub April 6, 2022. PMID: 35397952.

142. Makrakis D, Talukder R, Diamantopoulos LN, Lin GI, Carril-Ajuria L, Castellano D, De Kouchkovsky I, Koshkin VS, Park JJ, Alva A, Bilen MA, Stewart TF, McKay RR, Tripathi N, Agarwal N, Vather-W N, Jain J, Zakharia Y, Morales-Barrera R, Devitt ME, Cortellini A, Angela Maria FC, Pinato DJ, Nelson A, Hoimes CJ, Gupta K, Gartrell BA, Sankin A, Tripathi A, Zakopoulou R, Bamias A, Murgic J, Frobe A, Rodriguez-Vida A, Drakaki A, Liu S, Lu E, Kumar V, Di Lorenzo G, Joshi M, Isaacsson-Velho P, Buznego LA, Duran I, Moses M, Barata P, Sonpavde G, Yu EY, Montgomery RB, Grivas P, Khaki AR. Association between sites of metastasis and outcomes with immune checkpoint inhibitors in advanced urothelial carcinoma. *Clin Genitourin Cancer* 2022; 20(5):e440-e452. Epub June 5, 2022. PMID: 35778337.

143. Phuong A, Marquardt JP, O'Malley R, Holt SK, Laidlaw G, Eagle Z, Ngo S, Orcutt D, Schade GR, Lin DW, Schweizer MT, Yezefksi T, Yu EY, Montgomery B, Grivas P, Fintelmann FJ, Psutka SP. Changes in skeletal muscle and adipose tissue during cytotoxic chemotherapy for testicular germ cell carcinoma and associations with adverse events. *Urol Oncol* 2022; 40(10):456.e19-456.e30. Epub August 23, 2022. PMID: 36028450.

144. Sonpavde GP, Maughan BL, McGregor BA, Wei XX, Kilbridge KL, Lee RJ, Yu EY, Schweizer MT, Montgomery RB, Cheng HH, Hsieh AC, Jain R, Grewal JS, Pico-Navarro C, Gafoor Z, Perschy T, Grivas P. Phase II trial of CV301 vaccine combined with atezolizumab in advanced urothelial carcinoma. *Cancer Immunol Immunother* 2022; Epub August 23, 2022. PMID: 35998004.

145. Wong RL, Yu EY. Enfortumab vedotin in the treatment of urothelial cancers and beyond. *Future Oncol* 2022; 18(27):3067-3084. Epub August 25, 2022. PMID: 36004667.

146. Yu EY, Piulats JM, Gravis G, Fong PCC, Todenhofer T, Laguerre B, Arranz JA, Oudard S, Massard C, Heinzelbecker J, Nordquist LT, Carles J, Kolinsky MP, Augustin M, Gurney H, Tafreshi A, Li XT, Qiu P, Poehlein CH, Schloss C, De Bono JS. Pembrolizumab plus olaparib in patients with metastatic castrate-resistant prostate cancer: Long-term results from the Phase Ib/II KEYNOTE-365 Cohort A study. *Eur Urol* 2022; Epub August 30, 2022. PMID: 36055895.

147. Talukder R, Makrakis D, Lin GI, Diamantopoulos LN, Dawsey S, Gupta S, Carril-Ajuria L, Castellano D, De Kouchkovsky I, Koshkin VS, Park JJ, Alva A, Bilen MA, Stewart TF, McKay RR, Tripathi N, Agarwal N, Vather-Wu N, Zakharia Y, Morales-Barrera R, Devitt ME, Cortellini, Angela Maria FC, Pinato DJ, Nelson A, Hoimes CJ, Gupta K, Gartrell BA, Sankin A, Tripathi A, Zakopoulou R, Bamias A, Murgic J, Frobe A, Rodriguez-Vida A, Drakaki A, Liu S, Lu E, Kumar V, Di Lorenzo G, Joshi M, Isaacsson-Velho P, Buznego LA, Duran I, Moses M, Barata P, Sonpavde G, Wright JL, Yu EY, Montgomery RB, Grivas P, Khaki AR. Association of the time to immune checkpoint inhibitor initiation and outcomes with second line immune checkpoint inhibitor in patients with advanced urothelial carcinoma. *Clin Genitourin Cancer* 2022; 20(6):558-567. Epub August 19, 2022. PMID: 36155169.

148. Einerhand SMH, Black AJ, Zargar H, Fairey AS, Dinney CP, Mir MC, Krabbe LM, Cookson MS, Jacobson NE, Montgomery JS, Vasdev N, Yu EY, Xylinas E, Kassouf W, Dall'Era MA, Sridhar SS, McGrath JS, Aning J, Shariat SF, Wright JL, Thorpe AC, Morgan TM, Holzbeierlein JM, Bivalacqua TJ, North S, Barocas DA, Lotan Y, Grivas P, Garcia JA, Stephenson AJ, Shah JB, Daneshmand S, Spiess PE, van Rhijn BWG,* Black PC,* Mertens LS.* Multicenter evaluationa of neoadjuvant and induction gemcitabine-carboplatin versus gemcitabine-cisplatin followed by radical cystectomy for muscle-invasive bladder cancer. *World J Urol* 2022; 40(11):2707-2715. Epub September 28, 2022. PMID: 36169695. **Shared senior authorship.*

149. Gillessen S, Bossi A, Davis ID, de Bono J, Fizazi K, James ND, Mottet N, Shore N, Small E, Smith M, Sweeney C, Tombal B, Antonarakis ES, Aparicio AM, Armstrong AJ, Attard G, Beer TM, Beltran H, Bjartell A, Blanchard P, Briganti A, Bristow RG, Bulbul M, Caffo O, Castellano D, Castro E, Cheng HH, Chi KN, Chowdhury S, Clarke CS, Clarke N, Daugaard G, De Santis M, Duran I, Eeles R, Efstathiou E, Efstathiou J, Ekeke ON, Evans CP, Fanti S, Feng FY, Fonteyne V, Fossati N, Frydenberg M, George D, Gleave M, Gravis G, Halabi S, Heinrich D, Herrmann K, Higano C, Hofman MS, Horvath LG, Hussain M, Jereczek-Fossa BA, Jones R, Kanesvaran R, Kellokumpu-Lehtinen PL, Khauli RB, Klotz L, Kramer G, Leibowitz R, Logothetis CJ, Mahal BA, Maluf F, Mateo J, Matheson D, Mehra N, Merseburger A, Morgans AK, Morris MJ, Mrabti H, Mukherji D, Murphy DG, Murthy V, Nguyen PL, Oh WK, Ost P, O'Sullivan JM, Padhani AR, Pezaro C, Poon DMC, Pritchard CC, Rabah DM, Rathkopf D, Reiter RE, Rubin MA, Ryan CJ, Saad F, Sade JP, Sartor OA, Scher HI, Sharifi N, Skoneczna I, Soule H, Spratt DE, Srinivas S, Sternberg CN, Steuber T, Suzuki H, Sydes MR, Taplin ME, Tilki D, Turkeri L, Turco F, Uemura H, Uemura H, Urun Y, Vale CL, van Oort I, Vapiwala N, Walz J, Yamoah K, Ye D, Yu EY, Zapatero A, Zilli T, Omlin A. Management of patients with advanced prostate cancer. Part I: Intermediate-/high-risk and locally advanced disease, biochemical relapse, and side effects of hormonal treatment: Report of the Advanced Prostate Cancer Consensus Conference 2022. *Eur Urol* 2022; Epub December 6, 2022. PMID: 36494221.

150. Ghali F, Zhao Y, Patel D, Jewell T, Yu EY, Grivas P, Montgomery RB, Gore JL, Etzioni R, Wright JL. Surrogate endpoints as predictors of overall survival in metastatic bladder cancer: a trial level analysis. *Eur Urol Open Sci* 2023; Epub December 15, 2022. PMID: 36601043.

151. Schweizer MT, Gulati R, Yezefski T, Cheng HH, Mostaghel E, Haffner M, Patel R, De Sarkar N, Ha G, Dumpit R, Woo B, Lin A, Panlasigui P, McDonald N, Lai M, Nega K, Hammond J, Grivas P, Hsieh A, Montgomery B, Nelson P, Yu EY. Bipolar androgen therapy plus Olaparib in men with metastatic castration-resistant prostate cancer. *Prostate Cancer Prostatic Dis* 2023; Epub December 23, 2022. PMID: 36564459.

152. Makrakis D, Wright JL, Roudier MP, Garcia J, Vakar-Lopez F, Porter MP, Wang Y, Dash A, Lin D, Schade G, Winters B, Zhang X, Nelson P, Mostaghel E, Cheng HH, Schweizer M, Holt SK, Gore JL, Yu EY, Lam HM, Montgomery B. A phase 1/2 study of rapamycin and cisplatin/gemcitabine for treatment of patients with muscle-invasive bladder cancer. *Clin Genitourin Cancer* 2022; Epub December 23, 2022. PMID: ***.

153. Cheng HH, Sokolova AO, Gulati R, Bowen D, Grivas P, Hsieh A, Klemfuss N, Knerr S, Lee JK, Schweizer MT, Yezefski T, Zhou A, Yu EY, Nelson PS, Montgomery B. Internet-based germline genetic testing for men with metastatic prostate cancer. *JCO Precis Oncol* 2023; Epub January 2023. PMID: 36623239.

154. Crawford ED, Albala DM, Harris RG, Bryce AH, McKay RR, Carroll PR, Finkelstein SE, Garnick MB, Gomella LG, Higano CS, Koo PJ, Koo SJ, Petrylak DP, Sellinger SB, Slovin SF, Yu EY, Crosby M. A clinician's guide to targeted precision imaging in patients with prostate cancer (RADAR VI). *JU Open Plus* 2023; In press.

155. Kirk PS, Lotan T, Zargar H, Zargar K, Fairey AS, Dinney CA, Mir MC, Krabbe LM, Cookson MD, Jacobson NE, Montgomery JS, Vasdev N, Yu EY, Xylinas E, Kassouf W, Dall'Era MA, Sridhar SS, McGrath JS, Aning J, Shariat SF, Thorpe AC, Morgan TM, Holzbeierlein JM, Bivalacqua TJ, North S, Barocas DA, Grivas P, Garcia JA, Stephenson AJ, Shah JB, Daneshmand S, Spiess PE, van Rhijn BWG, Black P, Wright JL. Impact of maximal transurethral resection on pathological outcomes at cystectomy in a large, multi-institutional cohort. *J Urol* 2023; In press.

BOOK CHAPTERS

1. Yu EY, Hahn WC, George DJ, Kantoff PW. Opportunities for targeted molecular therapy for prostate cancer. In: Klein EA, editor. Management of prostate cancer. Totowa: Humana Press. 2004, Chapter 35:631-652.

2. Yu EY, Hahn WC. The origin of cancer. In: Farid NR, editor. Molecular basis of thyroid cancer. Norwell: Kluwer Academic Publishers. 2004, Chapter 1:1-22.

3. Yu EY. Hematology. In: Paauw DS, editor. Board basics, an enhancement to Medical Knowledge Self-Assessment Program (MKSAP 14). American College of Physicians. 2006, 104-119.

4. Yu EY. Oncology. In: Paauw DS, editor. Board basics, an enhancement to Medical Knowledge Self-Assessment Program (MKSAP 14). American College of Physicians. 2006, 171-190.

5. Jonasch E, Siefker-Radtke A, Yu EY, Higano CS, Tsu MS, Hey D, Thompson J. Genitourinary oncology. In: Lin EH, editor. 5th edition – a multidisciplinary cancer-matrix manual. Madison: Advanced Medical Publishing. 2010.

Videos

1. Protecting bone for men with prostate cancer. *Clinical Care Options*. 2011. http://www.clinicaloptions.com/Oncology/Management%20Series/Bone%20Health%202011/Interactive%20Virtual%20Presentations/Prostate%20Cancer%20IVP.aspx

2. New clinical perspectives for cancer care: optimizing therapeutic strategies targeting bone. *Clinical Care Options*. 2012. http://www.clinicaloptions.com/Oncology/Management%20Series/MD%20Bone%20Health/Downloadable%20Video%20Segments/Segment%201.aspx

3. Current and Emerging Therapies for the Treatment of Prostate Cancer (multidisciplinary case based discussion). *OncLive*. 2013. http://www.onclive.com/peer-exchange-archive/crpc-cases

4. Prognosis and prediction of outcomes in castration-resistant prostate cancer. *UroToday. 2013.* http://www.urotoday.com/index.php?option=com_content&Itemid=101&catid=1415&id=61828&lang=en&view=article

5. Role of PET imaging in prostate cancer. *OncLive TV*. November 14, 2013. http://www.onclive.com/onclive-tv/Dr-Yu-on-the-Role-of-PET-Imaging-in-Prostate-Cancer

6. Advances in treating mCRPC: Focus on immunotherapy – Measuring immune response in metastatic castration-resistant prostate cancer. *Elsevier Urology Journal*. 2014. http://www.webedcafe.com/extern/program_media/goldjournal.net/2014/URO2/figure.php?speaker=yu&figure=1

7. Free testosterone levels in men who have undergone orchiectomy. *OncLive TV*. February 6, 2014. https://www.youtube.com/watch?v=KaoHC3l8xvg

8. Utility of GTx-758 in metastatic castration-resistant prostate cancer. *OncLive*. February 24, 2014. https://www.onclive.com/onclive-tv/dr-yu-discusses-the-utility-of-gtx-758-in-mcrpc

9. Association of alkaline phosphatase with outcomes in chemotherapy-naïve patients with mCRPC. *OncLive*. May 1, 2014. https://www.youtube.com/watch?v=HF1rS1KEbl0

10. Exploring the heterogeneity of mCRPC and is clinical implications. *Peer Direct*. 2015. http://mp.pvupdate.com/player/50315/37325?pid=103068838#1

11. Expert perspectives – management of muscle-invasive bladder cancer. *OncLive*. 2015. http://www.onclive.com/insights/bladder-cancer

12. Selection of systemic therapy: Chemotherapy and androgen axis agents. *UroToday*. 2015. http://www.urotoday.com/media-gallery/493-selection-of-systemic-therapy-chemotherapy-and-androgen-axis-agents.html?category_id=1481

13. Smoking does not predispose to higher response rates with Atezolizumab – Imvigor 210 trial. *Oncology Tube*. 2016. http://www.oncologytube.com/v/1038465/smoking-does-not-predispose-higher-response-rate-to-atezolizumab-from-imvigor-210

14. Immunotherapy explained by Dr. Evan Yu. *Seattle Cancer Care Alliance*. February 27, 2017. https://www.youtube.com/watch?v=O-MhOSlpfDQ

15. Revolutionary advances for treating urothelial cancer. *OncLive*. April 21, 2017. http://www.onclive.com/inside-oncology/urothelial-carcinoma/revolutionary-advances-for-treating-urothelial-carcinoma

16. Personalizing therapy for advanced prostate cancer. *OncLive*. June 26, 2017. http://www.onclive.com/peer-exchange/personalizing-prostate-cancer-therapy

17. Metastatic prostate cancer: How to sequence newer agents. *ICAHO 2017*. September 19, 2017. https://www.youtube.com/watch?v=K-5SvhOoLcs

18. Should radium-223 be given earlier to metastatic prostate cancer patients? *Grand Rounds in Urology*. September 19, 2017.
http://www.grandroundsinurology.com/radium-223-given-earlier-metastatic-prostate-cancer-patients/?utm_campaign=Weekly%20Email%20GRU&utm_source=hs_email&utm_medium=email&utm_content=56497000&_hsenc=p2ANqtz-9_r8SC62R2rcSYyulPnl99iOicDkchgGiJe7rc4fAqHTTY_kJW2F3Px_ZhSqohqY5v0PZxJjYf0QaYI50OTg1pQ_Xylw&_hsmi=56497000

19. How to use combination, sequential and immune-oncology therapies in metastatic casetration resistant prostate cancer. *GU Connect*. December 4, 2017.
https://guconnect.info/entry/how-to-use-combination-sequential-and-immuno-oncology-therapies-in-mcrpc/

20. Clinical research in prostate cancer. *University of Washington Department of Medicine Grand Rounds.* January 11, 2018.
https://medicine.uw.edu/grand-rounds/clinical-research-prostate-cancer

21. Advances in the management of prostate cancer (Module 1). *Elsevier and ASIM*. February 15, 2018.
http://eocme.ads-staging.com/717a

22. Non-metastatic castration-resistant prostate cancer (M0 CRPC). *GU Connect.* February 20, 2018.
http://guconnect.info/entry/update-from-san-francisco-2018/

23. Comorbidities and therapy choice in prostate cancer. *Onclive TV*. June 6, 2018.
https://www.onclive.com/onclive-tv/dr-yu-on-comorbidities-and-therapy-choice-in-prostate-cancer

24. Treatment intensification in metastatic castration-sensitive prostate cancer. *OncLive TV*. June 25, 2018.
https://www.onclive.com/onclive-tv/dr-yu-on-treatment-intensification-in-metastatic-castrationsensitive-prostate-cancer

25. Advances in bladder cancer beyond immunotherapy and checkpoint inhibitors. *UroToday*. July 19, 2018.
https://www.urotoday.com/video-lectures/bladder-cancer/video/998-embedded-media2018-07-19-18-18-17.html

26. The future of castration-sensitive prostate cancer. *OncLive TV*. August 1, 2018.
https://www.onclive.com/onclive-tv/dr-yu-on-the-future-of-castrationsensitive-prostate-cancer

27. Metastatic prostate cancer: How to sequence newer agents. *VuMedi*. August, 2018.
https://www.vumedi.com/video/metastatic-prostate-cancer-how-to-sequence-newer-agents/?utm_campaign=Metastatic+Prostate+Cancer%3A+How+to+Sequence+Newer+Agents&utm_term=Prostate&utm_content=Metastatic+Prostate+Cancer%3A+How+to+Sequence+Newer+Agents&utm_source=Users-GU_35425&mail_id=35425&token=04e15778-a8b6-4962-a719-15c26cf023c8&utm_medium=Video

28. KEYNOTE-057 trial for high-risk non-muscle invasive bladder cancer. *UroToday*. November 2018.
https://www.urotoday.com/video-lectures/esmo-2018/video/mediaitem/1071-embedded-media2018-11-05-01-42-21.html?utm_source=newsletter_6002&utm_medium=email&utm_campaign=uroalerts-oncology-daily

29. Radium-223 as bone targeted therapy for castration resistant prostate cancer. *OncLive Insights*. December 21, 2018.
https://www.onclive.com/insights/best-practices-metastatic-prostate-cancer/radium-223-as-bone-targeted-therapy-for-crpc?utm_medium=email&utm_campaign=ONCSS%20US%20Prostate%20Insights%20-%20Xofigo%20Bayer%20%201-22-19&utm_content=ONCSS%20US%20Prostate%20Insights%20-%20Xofigo%20Bayer%20%201-22-19+CID_1d7357a330fbbd14b99edaa0b83f5aa1&utm_source=CM%20ONCLIVE&utm_term=Radium-223%20as%20Bone-Targeted%20Therapy%20for%20CRPC

30. Further therapeutic strategies in metastatic castration resistant prostate cancer. *OncLive Insights*. December 21, 2018.
https://www.onclive.com/insights/best-practices-metastatic-prostate-cancer/further-therapeutic-strategies-in-metastatic-crpc

31. Practical applications of ERA 223 in the metastatic castration resistant prostate cancer paradigm. *OncLive Insights*. December 21, 2018.
https://www.onclive.com/insights/best-practices-metastatic-prostate-cancer/practical-applications-of-era-223-in-the-mcrpc-paradigm

32. Role of PARP inhibitors in prostate cancer. *Urotoday*. January 30, 2019.
https://www.urotoday.com/video-lectures/prostate-cancer-foundation/video/1137-embedded-media2019-01-30-18-44-51.html

33. KEYNOTE-365 Cohort A: Pembrolizumab plus olaparib in docetaxel-pretreated patients with metastatic castration-resistant prostate cancer. *eCancerTV*. February 18, 2019.
https://ecancer.org/video/7697/keynote-365-cohort-a--pembrolizumab-plus-olaparib-in-docetaxel-pretreated-patients-with-mcrpc.php

34. Combination therapy for patients with metastatic prostate cancer. *OncLive TV*. February 14, 2019.
https://www.onclive.com/onclive-tv/dr-yu-on-combination-therapy-for-patients-with-metastatic-prostate-cancer

35. Results from KEYNOTE-365 in metastatic castration resistant prostate cancer. *OBRoncology*. February 22, 2019.
https://www.youtube.com/watch?v=jJm_DQrHwIc

36. Combining checkpoint inhibitors in metastatic castration-resistant prostate cancer. *OBRoncology*. February 22, 2019.
https://www.youtube.com/watch?v=zkOR1bmmS0w

37. Treatment strategies for patients with oligometastatic prostate cancer. *OncLive TV.* February 22, 2019.
https://www.onclive.com/onclive-tv/dr-yu-discusses-treatment-strategies-for-patients-with-oligometastatic-prostate-cancer

38. Unexpected responses to prostate cancer treatments. *2019 Prostate Cancer Research Institute Excerpts*. March 6, 2019.
https://www.youtube.com/watch?v=-L2VMfwOTlE

39. Results from KEYNOTE 365 in metastatic castration-resistant prostate cancer. *OncologyTube*. March 20, 2019.
https://www.oncologytube.com/video/results-from-keynote-365-in-mcrpc/10006094?utm_campaign=Ninlaro&utm_source=hs_email&utm_medium=email&utm_content=71681800&_hsenc=p2ANqtz--i1KSQwltChCOA9gH-m8dtsEtgG3P5druSdA4s3a-n4Ms6BfvDsIB71JsyflptFwYYW3LDzWPEWcwcYwWR61C9OLbHCA&_hsmi=71681800

40. Sequencing treatments in metastatic prostate cancer. *Urotoday*. April 11, 2019.
https://www.urotoday.com/video-lectures/crpc-w-bone-metastases/video/1231-embedded-media2019-04-11-12-37-41.html

41. Prostate cancer highlights from ASCO 2019. *COR2ED*. June 4, 2019.
https://vimeo.com/340228105

42. Advances in bladder cancer beyond immunotherapy and checkpoint inhibitors. *UroToday.* Jun 18, 2019.
https://www.urotoday.com/video-lectures/advanced-bladder-cancer/video/mediaitem/998-embedded-media2018-07-19-18-18-17.html

43. Combining pembrolizumab and olaparib in metastatic castration-resistant prostate cancer. *OncLive TV*. June 21, 2019.
https://www.onclive.com/onclive-tv/dr-yu-on-combining-pembrolizumab-and-olaparib-in-mcrpc

44. Management of metastatic castration resistant prostate cancer using Sipuleucel-T. *Urotoday*. June 23, 2019.
https://www.urotoday.com/video-lectures/asco-2019/video/1337-players-brightcove-net2019-06-12-18-29-47.html

45. Optimal drug sequencing in metastatic castration-resistant prostate cancer. *UroToday*. May 5, 2020.
https://www.urotoday.com/video-lectures/mcrpc-treatment/video/mediaitem/1740-optimal-drug-sequencing-in-metastatic-castration-resistant-prostate-cancer-mcrpc-evan-yu.html?utm_source=newsletter_7804&utm_medium=email&utm_campaign=real-world-sequencing-in-metastatic-castration-resistant-prostate-cancer-treatment

46. Treatment advances in non-metastatic castration-resistant prostate cancer. *UroToday*. May 16, 2020.
https://www.urotoday.com/video-lectures/nmcrpc/video/mediaitem/1739-treatment-advances-in-non-metastatic-castration-resistant-prostate-cancer-evan-yu.html

47. Significant impact of COVID-19 on the treatment of metastatic castration-resistant prostate cancer. *Targeted Oncology*. June 2, 2020. https://www.targetedonc.com/view/case-review-rationale-and-methods-in-mcrpc?seriesVid=5

48. Rapidly expanding options in metastatic castration resistant prostate cancer. *Targeted Oncology*. June 2, 2020. https://www.targetedonc.com/view/rapidly-expanding-options-in-mcrpc

49. Setting realistic goals with palliative therapy in metastatic castration resistant prostate cancer. *Targeted Oncology*. June 2, 2020. https://www.targetedonc.com/view/setting-realistic-goals-with-palliative-therapy-in-mcrpc

50. Pragmatic considerations for early radium-223 in metastatic castration resistant prostate cancer. *Targeted Oncology*. June 2, 2020. https://www.targetedonc.com/view/pragmatic-considerations-for-early-radium-223-in-mcrpc

51. Therapeutic options for patients with metastatic hormone-sensitive prostate cancer. *Urotoday*. June 26, 2020. https://www.urotoday.com/video-lectures/mhspc/video/1702-therapeutic-options-for-patients-with-metastatic-hormone-sensitive-prostate-cancer-evan-yu.html

52. Metastatic castration-sensitive prostate cancer: New treatment options. *UroToday.* August 2020. https://www.urotoday.com/video-lectures/mhspc/video/mediaitem/1702-therapeutic-options-for-patients-with-metastatic-hormone-sensitive-prostate-cancer-evan-yu.html

53. TRITON2 Sound bite. *Vimeo.* August 19, 2020. https://vimeo.com/448677356/e1fc46a42c

54. GU Connect Masterclass. *Vimeo.* October 23, 2020. https://vimeo.com/471323786

55. Increasing awareness of nonmetastatic (M0) castration-resistant prostate cancer. *OncLive*. November 23, 2020. https://www.onclive.com/view/prostate-cancer-chaired-by-evan-y-yu-md

56. What is the role of chemotherapy in modern day prostate cancer treatment? *Youtube.* March 3, 2021. https://www.youtube.com/watch?v=wKP0QkhMTXQ

57. PSMA PET imaging in prostate cancer. *Urology Times*. March 8, 2021. https://www.urologytimes.com/view/dr-evan-yu-on-psma-pet-imaging-in-prostate-cancer

58. Immunotherapy's role in prostate cancer. *Prostate Cancer Research Institute.* June 14, 2021. https://www.youtube.com/watch?v=5_lCcMWL3l4

59. Germline vs. somatic testing in prostate cancer. *Prostate Cancer Research Institute*. July 6, 2021. https://www.youtube.com/watch?v=4vSYS50PQrQ

60. Phenotypic expression of prostate specific membrane antigen. *Uro-Today*. July 20, 2021. https://www.urotoday.com/video-lectures/phenotypic-precision-medicine/video/2219-phenotypic-expression-of-prostate-specific-membrane-antigen-psma-evan-yu.html

61. Role of precision medicine in PSMA-positive metastatic castration-resistant prostate cancer. *Targeted Oncology*. August 20, 2021. https://www.targetedonc.com/view/role-of-precision-medicine-in-psma-positive-mcrpc

62. PSMA-Positive metastatic castration-resistant prostate cancer: Phase 3 VISION Trial. *Targeted Oncology*. August 20, 2021. https://www.targetedonc.com/view/psma-positive-mcrpc-phase-3-vision-trial

63. Patient response to LuPSMA therapy in metastatic castration-resistant prostate cancer. *Targeted Oncology*. August 20, 2021. https://www.targetedonc.com/view/patient-response-to-lupsma-therapy-in-mcrpc

64. Phase 2 TheraP trial in PSMA-positive metastatic castration-resistant prostate cancer. *Targeted Oncology*. August 20, 2021. https://www.targetedonc.com/view/phase-2-therap-trial-in-psma-positive-mcrpc

65. Sequencing of LuPSMA therapy in PSMA-positive metastatic castration-resistant prostate cancer. *Targeted Oncology*. August 20, 2021. https://www.targetedonc.com/view/sequencing-of-lupsma-therapy-in-psma-positive-mcrpc

66. Utility of enfortumab vedotin in metastatic urothelial cancer. *OncLive*. November 12, 2021. https://www.onclive.com/view/dr-yu-on-the-utility-of-enfortumab-vedotin-in-metastatic-urothelial-cancer

67. Factors in selective novel AR-targeted therapy for nonmetastatic castration resistant prostate cancer. *OncLive*. April 6, 2022. https://www.onclive.com/view/factors-in-selecting-novel-ar-targeted-therapy-for-nonmetastatic-crpc

68. Monitoring strategies in nonmetastatic castration resistant prostate cancer. *OncLive.* April 13, 2022. https://www.onclive.com/view/monitoring-strategies-in-nonmetastatic-crpc

69. Overview of therapy for metastatic castration resistant prostate cancer. *OncLive.* May 4, 2022. https://www.onclive.com/view/overview-of-therapy-for-mcrpc-parp-inhibitors

70. Selecting among novel imaging options in metastatic castration resistant prostate cancer. *OncLive.* May 11, 2022. https://www.onclive.com/view/selecting-among-novel-imaging-options-in-metastatic-crpc

71. Addressing bone and visceral metastases in metastatic castration resistant prostate cancer. *OncLive.* May 18, 2022. https://www.onclive.com/view/addressing-bone-and-visceral-metastases-in-metastatic-crpc

72. Phenotypic precision medicine and its role in genitourinary oncology – Part 1. *GU Onc Now*. May 20, 2022.
https://www.youtube.com/watch?v=lka_chk4fqM

73. Phenotypic precision medicine and its role in genitourinary oncology – Part 2. *GU Onc Now*. May 20, 2022.
https://www.youtube.com/watch?v=IBN8rWNfF5c

74. Prostate cancer management: Future directions in care. *OncLive*. May 25, 2022.
https://www.onclive.com/view/prostate-cancer-management-future-directions-in-care

75. Clinical Scenario 1: A 67-year-old with metastatic hormone sensitive prostate cancer. *OncLive.* June 28, 2022.
https://www.onclive.com/view/clinical-scenario-1-a-67-year-old-with-metastatic-hspc

76. Optimizing management of metastatic hormone sensitive prostate cancer: Multimodality care and genetic testing. *OncLive.* June 28, 2022.
https://www.onclive.com/view/optimizing-management-of-mhspc-multimodality-care-and-genetic-testing

77. Factors in selecting Androgen Receptor-targeted therapy for patients with metastatic hormone sensitive prostate cancer. *OncLive*. July 5, 2022.
https://www.onclive.com/view/factors-in-selecting-ar-targeted-therapy-for-patients-with-metastatic-hspc

78. Establishing eligibility for frontline Androgen Receptor-targeted therapy in metastatic hormone sensitive prostate cancer. *OncLive*. July 5, 2022.
https://www.onclive.com/view/establishing-eligibility-for-frontline-ar-targeted-therapy-in-mhspc

79. Clinical trial data in metastatic hormone-sensitive prostate cancer from the ASCO 2022 Annual Meeting. *OncLive.* July 12, 2022.
https://www.onclive.com/view/clinical-trial-data-in-metastatic-hspc-from-the-asco-2022-annual-meeting

80. Improving patient monitoring in the setting of metastatic hormone-sensitive prostate cancer. *OncLive.* July 12, 2022.
https://www.onclive.com/view/improving-patient-monitoring-in-the-setting-of-metastatic-hspc

81. Clinical Scenario 2: A 64-year-old man with non-metastatic castration-resistant prostate cancer. *OncLive.* July 19, 2022.
https://www.onclive.com/view/clinical-scenario-2-a-64-year-old-man-with-nmcrpc

82. Optimizing management of non-metastatic castration-resistant prostate cancer: Patient monitoring and initiating therapy. *OncLive*. July 19, 2022.
https://www.onclive.com/view/optimizing-management-of-nmcrpc-patient-monitoring-and-initiating-therapy

83. ASCO 2022 prostate cancer updates. *YouTube - Total Health Conferencing.* July 26, 2022.

https://www.youtube.com/watch?v=QA8znw4ClpA

84. Selecting among available Androgen Receptor inhibitors in non-metastatic castration-resistant prostate cancer. *OncLive.* July 26, 2022. https://www.onclive.com/view/selecting-among-available-ar-inhibitors-in-nonmetastatic-cprc

85. Addressing unmet needs in non-metastatic castration-resistant prostate cancer. *OncLive.* July 26, 2022. https://www.onclive.com/view/addressing-unmet-needs-in-nonmetastatic-crpc

86. Clinical Scenario 3: A 76-year-old with metastatic castration-resistant prostate cancer. *OncLive.* August 2, 2022. https://www.onclive.com/view/clinical-scenario-3-a-76-year-old-with-metastatic-crpc

87. Metastatic castration-resistant prostate cancer: Optimal imaging strategies. *OncLive.* August 2, 2022. https://www.onclive.com/view/metastatic-castration-resistant-prostate-cancer-optimal-imaging-strategies

88. Therapy overview: Sequencing agents in patients with metastatic castration-resistant prostate cancer. *OncLive.* August 9, 2022. https://www.onclive.com/view/therapy-overview-sequencing-agents-in-patients-with-metastatic-crpc

89. PTEN loss in metastatic castration-resistant prostate cancer: Caution surrounding mTOR, PI3K, and AKT inhibition. *OncLive.* August 9, 2022. https://www.onclive.com/view/pten-loss-in-mcrpc-caution-surrounding-mtor-pi3k-and-akt-inhibition

90. An overview of PARP inhibition in metastatic castration resistant prostate cancer. *OncLive*. August 16, 2022. https://www.onclive.com/view/an-overview-of-parp-inhibition-in-metastatic-crpc

91. Metastatic castration resistant prostate cancer: Practical selection and use of PARP inhibitors. *OncLive*. August 16, 2022. https://www.onclive.com/view/metastatic-crpc-practical-selection-and-use-of-parp-inhibitors

92. What is the role of ^{177}Lu-PSMA-617 in metastatic castration-resistante prostate cancer. *OncLive*. August 23, 2022. https://www.onclive.com/view/what-is-the-role-of-177lu-psma-617-in-metastatic-crpc-

93. Practical consideration in selecting therapy for metastatic castration-resistant prostate cancer. *OncLive*. August 23, 2022. https://www.onclive.com/view/practical-considerations-in-selecting-therapy-for-metastatic-crpc

REVIEWS, EDITORIALS, COMMENTARIES AND OTHER PUBLICATIONS

1. Yu EY, Oh WK. Neoadjuvant therapy for high-risk localized prostate cancer. *Curr Oncol Rep* 2003; 5(3):250-257. PMID: 12667424. [invited review]

2. Yu EY. Commentary: Highlights in prostate cancer from the 2011 American Urological Association annual meeting and the 2011 American Society of Clinical Oncology annual meeting. *Clin Adv Hematol Oncol* 2011; 9(8), supplement 21:1-24. PMID: 22362073. [invited commentary]

3. Yu EY. Castration-resistant prostate cancer: Novel targets, agents and trials. 2012 Genitourinary Cancers Symposium Educational Book. February 2012. [invited review]

4. Cheng HH, Lin DW, Yu EY. Advanced clinical states in prostate cancer. *Urol Clin North Am* 2012; 39(4):561-571. Epub September 12, 2012. PMID: 23084531. [invited review]

5. Yu EY. News & Views Commentary: Prostate cancer Bone density testing – essential or extraneous? *Nat Rev Urol* 2012; 10(1):11-12. Epub December 11, 2012. PMID: 23229500. [invited commentary]

6. Zhao S, Yu EY. Castrate-resistant prostate cancer: postdocetaxel management. *Curr Opin Urol* 2013; 23(3):201-207. Epub January 22, 2013. PMID: 23344012. PMCID: 4486479. NIHMSID: 700751. [invited review]

7. Derleth CL, Yu EY. Targeted therapy in the treatment of castration-resistant prostate cancer. *Oncology* 2013; 27(7):620-628. Epub July 15, 2013. PMID: 23977754. [invited review]

8. Wu JD, Yu EY. Insulin-like growth factor receptor-1 (IGF-IR) as a target for prostate cancer therapy. *Cancer Metastasis Rev* 2014; 33(2-3):607-613. Epub January 12, 2014. PMID: 24414227. PMCID: 4096322. NIHMSID: 549687. [invited review]

9. Yu EY, Oh WK. Editorial (guest editor for special prostate cancer issue): The metastatic castration-resistant prostate cancer treatment paradigm: more choices, more questions. *Asian J Androl* 2014; 16(3):331-333. PMID: 24759585. PMCID: 4023355. [invited editorial]

10. Ramos JD, Cheng HH, Yu EY. Long-term survival in bone-predominant metastatic urothelial carcinoma. *Clin Genitourin Cancer* 2014; 12(6):e241-e244. Epub July 23, 2014. PMID: 25160520. PMCID: 4252264. NIHMSID: 616357. [original case series]

11. Cowan AJ, Inoue Y, Yu EY. Delayed antiandrogen withdrawal syndrome after discontinuation of bicalutamide. *Clin Genitourin Cancer* 2014; 13(1):e51-e53. Epub September 22, 2014. PMID: 25450034. PMCID: 4289435. NIHMSID: 636853. [original case series]

12. Ramos JD, Yu EY. Progress in understanding what is being statin(ed) in prostate cancer. *JAMA Oncology* 2015; 1(4):428-430. Epub May 7, 2015. PMID: 26181247. PMCID: 5344994. NIHMISID: 829581. [invited commentary]

13. Ramos JD, Yu EY. Cardiovascular mortality in testicular nonseminoma germ cell tumors: does statistical significance imply clinical significance? *J Clin Oncol* 2015; 33(28):3075-3077. Epub August 24, 2015. PMID: 26304903. PMCID: 5433521. [invited commentary]

14. Schweizer MT, Yu EY. Persistent androgen receptor addiction in castration-resistant prostate cancer. *J Hematol Oncol* 2015; 8(1):128. Epub November 13, 2015. PMID: 26566796. PMCID: 4644296. [invited review]

15. Schweizer MT, Yu EY. Targeting intratumoral androgens: Statins and beyond. *Ther Adv Med Oncol* 2016; 8(5):388-395. Epub May 11, 2016. PMID: 27583031. PMCID: 4981288. [invited review]

16. Yu EY, Lin DW. Avoiding under-treatment of aggressive prostate cancer by considering early use of chemotherapy. *JAMA Oncol* 2017; 3(1):13-14. Epub November 3, 2016. PMID: 27812683. [invited point counterpoint]

17. Ramos JD, Yu EY. Making urothelial carcinomas less immune to immunotherapy. *Urol Oncol* 2016; 34(12):534-537. Epub November 8, 2016. PMID: 27836245. PMCID: 5402727. [invited editorial]

18. Schweizer MT, Yu EY. Androgen receptor signaling in human malignancies: Prostate cancer and beyond. *Cancers* 2017; 9(1). Epub January 11, 2017. PMID: 28085048. PMCID: 5295778. [invited review]

19. Ramos JD, Yu EY. Letter to the Editor Re: Incidence, characteristics and implications of thromboembolic events in patients with muscle invasive urothelial carcinoma of the bladder undergoing neoadjuvant chemotherapy. *J Urol* 2017; 197(5):1360-1362. Epub February 7, 2017. PMID: 28183523. [letter to the editor]

20. Ramos JD, Yu EY. Immuno-oncology in urothelial carcinoma: who or what will ultimately sit on the iron throne. *Immunotherapy* 2017; 9(12):951-954. PMID: 28971748. [invited review]

21. Dietrich B, Siefker-Radtke AO, Srinivas S, Yu EY. Systemic therapy for advanced urothelial carcinoma: Current standards and treatment considerations. *Am Soc Clin Oncol Educ Book* 2018; May 23; (38):342-353. PMID: 30231356. [invited review]

22. Koshkin VS, O'Donnell P, Yu EY, Grivas P. Targeting HER2 in bladder cancer. *Bladder Cancer* 2019; 5(1):1-12. [invited review]

23. Aragon-Ching JB, Choudhury A, Margulis V, Yu EY. Formidable scenarios in urothelial and variant cancers of the urinary tract. *Am Soc Clin Oncol Educ Book* 2019; 39:262-275. PMID: 31099661. [invited review]

24. Grivas P, Yu EY. Role of targeted therapies in management of metastatic urothelial cancer in the era of immunotherapy. *Curr Treat Options Oncol* 2019; 20(8):67. PMID: 31254108. [invited review]

25. Schweizer MT, Yu EY. "Matching" the "mismatch" repair deficient prostate cancer with immunotherapy. *Clin Cancer Res* 2020; 26(5):981-983. Epub January 3, 2020. PMID: 31900277. PMCID: 7123990. [invited commentary]

26. Schiff JP, Barata PC, Yu EY, Grivas P. Precision therapy in advanced urothelial cancer. *Expert Rev Precis Med Drug Dev* 2019; 4(2):81-93. Epub March 5, 2019. [invited review]

27. Sokolova AO, Yu EY, Cheng HH. Honing in on PARPi response in prostate cancer: from HR pathway- to gene-by-gene granularity. *Clin Cancer Res* 2020; 26(11):2439-2440. Epub March 31, 2020. PMID: 32234758. PMCID: 7269828. [invited commentary]

28. Wong RL, Yu EY. Refining immune-oncology approaches in metastatic prostate cancer: Transcending current limitations. *Curr Treat Options Oncol* 2020; 22(2):13. Epub January 12, 2021. PMID: 33433743. [invited review]

29. Lee RJ, Madan RA, Kim J, Posadas EM, Yu EY. Disparities in cancer care and the Asian American population. *Oncologist* 2021; Epub March 8, 2021. PMID: 33683795. PMCID: 8176990. [invited commentary]

30. Kamat NV, Yu EY, Lee JK. BiTE-ing into prostate cancer with bispecific T cell engagers. *Clin Cancer Res* 2021; 27(10):2675-2677. Epub March 11, 2021. PMID: 33707179. PMCID: 8127346. [invited commentary]

On-line Publications

1. Yu EY, Corey E. Beyond the abstract – Dasatinib inhibits the growth of prostate cancer in bone and provides additional protection from osteolysis. Uro-Today. On-line, December 17, 2009.

2. Yu EY. Editor's Note – Evan Yu introduces Clinical Trials Portal. Uro-Today. On-line, December 15, 2016.

3. Yu EY. From the Desk of Evan Yu – Homologous recombination deficiency in metastatic prostate cancer. Uro-Today. On-line, February 12, 2017.

4. Yu EY. Non-metastatic castration-resistant prostate cancer, a disease state misnomer that is a seriously unmet therapeutic need. Uro-Today. On-line, March 14, 2017.

5. Yu EY. From the Desk of Evan Yu: PD-1 or PD-L1 inhibition for front-line metastatic urothelial cancer. Uro-Today. On-line, April 11, 2017.

6. Yu EY. From the Desk of Evan Yu: No…the ball game is not over…adjuvant trials of PD-1 and PD-L1 antibodies in urothelial carcinoma must go on! Uro-Today. On-line, May 18, 2017.

7. Yu EY. From the Desk of Evan Yu: What should I do with my new metastatic clear cell renal carcinoma patients? Uro-Today. On-line, June 8, 2017.

8. Yu EY. From the Desk of Evan Yu: Another advance in metastatic hormone-sensitive prostate cancer may change standard of care options but not attitude toward clinical trials. Uro-Today. On-line, July 14, 2017.

9. Yu EY. From the Desk of Evan Yu: Does PD-1/PD-L1 inhibition really work in prostate cancer? Uro-Today. On-line, August 14, 2017.

10. Yu EY. From the Desk of Evan Yu: Are there clinical trials for relapsed/refractory germ cell tumors? Uro-Today. On-line, September 8, 2017.

11. Yu EY. From the Desk of Evan Yu: Options for cisplatin-ineligible patients with muscle invasive localized urothelial carcinoma. Uro-Today. On-line, October 28, 2017.

12. Yu EY. From the Desk of Evan Yu: Radium-223, looking for a dance partner. Uro-Today. On-line, November 10, 2017.

13. Yu EY. From the Desk of Evan Yu: Fibroblast growth factor receptors (FGFRs), a new hope for patients with urothelial carcinomas. Uro-Today. On-line, December 6, 2017.

14. Yu EY. From the Desk of Evan Yu: If not 1st line, how about creating a 1.5 line therapy for metastatic urothelial carcinoma. Uro-Today. On-line, January 1, 2018.

15. Yu EY. From the Desk of Evan Yu: Taking out the Tregs by inhibiting IDO1. Uro-Today. On-line, February 1, 2018.

16. Yu EY. From the Desk of Evan Yu: With apalutamide's regulatory approval for non-metastatic (M0) CRPC, why not move agents even earlier in the castration-sensitive biochemically-recurrent disease state? Uro-Today. On-line, March 1, 2018.

17. Yu EY. From the Desk of Evan Yu: Antibody drug conjugates for urothelial carcinoma, a cool technology with promising results. Uro-Today. On-line, April 2, 2018.

18. Yu EY. From the Desk of Evan Yu: Intervening on active surveillance of prostate cancer. Uro-Today. On-line, June 4, 2018.

19. Yu EY. From the Desk of Evan Yu: PARP inhibition for uorthelial carcinoma…enrichment or combinations? Uro-Today. On-line, June 18, 2018.

20. Yu EY. From the Desk of Evan Yu: How can I keep my bladder, doc? The BCG refractory non-muscle invasive bladder cancer quetion. Uro-Today. On-line, July 9, 2018.

21. Yu EY. From the Desk of Evan Yu: Adjuvant therapy for renal cell carcinoma? Uro-Today. On-line, August 3, 2018.

22. Yu EY. From the Desk of Evan Yu: Why aren't there more systemic therapy trials for patients with muscle-invasive urothelial carcinoma of the bladder? Uro-Today. On-line, September 6, 2018.

23. Yu EY. From the Desk of Evan Yu: Prostate-specific membrane antigen (PSMA)-targeted radioligand therapies are finally arriving. Uro-Today. On-line, October 1, 2018.

24. Yu EY. From the Desk of Evan Yu: Sipuleucel-T…Beyond the IMPACT trial. Uro-Today. On-line, November 5, 2018.

25. Yu EY. From the Desk of Evan Yu: Are more indications for local therapy of prostate cancer on the horizon. Uro-Today. On-line, December 12, 2018.

26. Yu EY. From the Desk of Evan Yu: Clinical trial updates of single-agent PARP inhibitor use in homologous recombination deficient prostate cancer populations. Uro-Today. On-line, January 7, 2019.

27. Yu EY. From the Desk of Evan Yu: Is testosterone such a bad thing for prostate cancer? Rationale for using supraphysiologic testosterone to treat castration-resistant prostate cancer. Uro-Today. On-line, February 8, 2019.

28. Yu EY. From the Desk of Evan Yu: PARP with PD-1/PD-L1 inhibition. Is there any magic to the combination in a molecularly unselected patient population. Uro-Today. On-line, February 15, 2019.

29. Yu EY. From the Desk of Evan Yu: Fluciclovine (Axumin®) PET/CT imaging in prostate cancer: More uses than just for recurrent disease? Uro-Today. On-line, March 13, 2019.

30. Yu EY. From the Desk of Evan Yu: The next step in bladder cancer immune-Oncology therapy? Combination Therapy! Uro-Today. On-line, April 17, 2019.

31. Yu EY. From the Desk of Evan Yu: Androgen receptor mutations in prostate cancer; A worthwhile therapeutic target? Uro-Today. On-line, May 15, 2019.

32. Yu EY. From the Desk of Evan Yu: Enzalutamide and Apalutamide now offer survival benefit for patients with metastatic castration-sensitive prostate cancer, but how do things change now and what should we be doing next? Uro-Today. On-line, June 12, 2019.

33. Yu EY. From the Desk of Evan Yu: Heating things up in a volatile marriage…bispecific antibody therapy in prostate cancer. Uro-Today. On-line, July 9, 2019.

34. Yu EY. From the Desk of Evan Yu: Polycomb complex enhancer of zeste 2 (EZH2), a regulator of lineage reprogramming and a new drug target. Uro-Today. On-line, August 9, 2019.

35. Yu EY. From the Desk of Evan Yu: Is HER2 still a worthwhile therapeutic target for urothelial bladder cancer? Uro-Today. On-line, September 16, 2019.

36. Yu EY. ESMO 2019 Highlights: Overall survival interim analysis results of the phase 3 SPARTAN trial. Uro-Today. On-line, October 2, 2019.

37. Yu EY. ESMO 2019 Highlights: Invited Discussant: IMvigor 130: Phase III study of atezolizumab with or without platinum-based chemotherapy in previously untreated metastatic urothelial carcinoma. Uro-Today. On-line, October 2, 2019.

38. Yu EY. ESMO 2019 Highlights: Enfortumab vedotin plus pembrolizumab for urothelial carcinoma. Uro-Today. On-line, October 2, 2019.

39. Yu EY. From the Desk of Evan Yu: What works for breast cancer should work for prostate cancer, right? Uro-Today. On-line, October 9, 2019.

40. Yu EY. From the Desk of Evan Yu: The CARD trial creates a new standard…for certain patients. Uro-Today. On-line, November 9, 2019.

41. Yu EY. From the Desk of Evan Yu: Is chemoimmunotherapy prime time for first-line metastatic urothelial carcinoma. Uro-Today. On-line, December 17, 2019.

42. Yu EY. From the Desk of Evan Yu: ^{177}Lutetium-PSMA-617 in metastatic castration-resistant prostate cancer: Randomized phase 3 trial data is pending and novel combinations are being tested. Uro-Today. On-line, January 6, 2020.

43. Yu EY. From the Desk of Evan Yu: Neoadjuvant systemic therapy for prostate cancer: If a PUNCH is good, what will it take to score a knockout? Uro-Today. On-line, February 7, 2020.

44. Yu EY. From the Desk of Evan Yu: Enfortumab vedotin – Changing the way we think about urothelial cancer. Uro-Today. On-line, March 3, 2020.

45. Yu EY. From the Desk of Evan Yu: Neuroendocrine carcinomas of the genitourinary tract – treatment options are desperately needed…even during the COVID-19 pandemic. Uro-Today. On-line, March 31, 2020.

46. Yu EY. From the Desk of Evan Yu: Are chimeric antigen recept (CAR)-T cells ready for prime time in prostate cancer? Uro-Today. On-line, April 29, 2020.

47. Yu EY. From the Desk of Evan Yu: The oligometastatic-directed therapy trend in prostate cancer: Are we being precocious or premature? Uro-Today. On-line, June 5, 2020.

48. Yu EY. From the Desk of Evan Yu: Combination therapy with docetaxel for metastatic castration-resistant prostate cancer – new drugs with new promise? Uro-Today. On-line, July 1, 2020.

49. Yu EY. From the Desk of Evan Yu: Improving on cabazitaxel chemotherapy for metastatic prostate cancer – studying novel combinations. Uro-Today. On-line, August 2, 2020.

50. Yu EY. From the Desk of Evan Yu: Prostate cancer imaging is changing rapidly – what more should be done with Fluciclovine (Axumin®) PET/CT imaging? Uro-Today. On-line, September 1, 2020.

51. Yu EY. From the Desk of Evan Yu: What's the rationale for adding PARP inhibitors to androgen pathway inhibitors for patients with prostate cancer? Uro-Today. On-line, October 1, 2020.

52. Yu EY. From the Desk of Evan Yu: Erdafitinib, potential for expanding indications for the future. Uro-Today. On-line, November 2, 2020.

53. Yu EY. From the Desk of Evan Yu: Cabozantinib for prostate cancer – A renewed hope. Uro-Today. On-line, November 30, 2020.

54. Yu EY. From the Desk of Evan Yu: PI3K/AKT/mTOR inhibitors for prostate cancer – Finally hints of a breakthrough. Uro-Today. On-line, January 5, 2021.

55. Yu EY. From the Desk of Evan Yu: Sacituzumab govitecan – Another antibody drug conjugate carving out a path in genitourinary oncology. Uro-Today. On-line, February 1, 2021.

56. Yu EY. From the Desk of Evan Yu: Will immunotherapy work as salvage therapy for patients with testicular germ cell tumors. Uro-Today. On-line, March 1, 2021.

57. Wong RL and Yu EY. Refining immuno-oncology approaches in metastatic prostate cancer: Transcending current limitations – Beyond the Abstract. Uro-Today. On-line, March 31, 2021.

58. Yu EY. From the Desk of Evan Yu: Is adjuvant therapy a new standard for urothelial carcinoma? Uro-Today. On-line, April 1, 2021.

59. Yu EY. From the Desk of Evan Yu: Partnering up with abiraterone acetate – Potentials for a harmonious relationship. Uro-Today. On-line, May 3, 2021.

60. Yu EY. From the Desk of Evan Yu: Adenosine Triphosphate (ATP), energy for your cells, but inflammatory towards cancer. Uro-Today. On-line, June 8, 2021.

61. Yu EY. From the Desk of Evan Yu: ^{177}Lutetium-PSMA-617, the newest life-prolonging therapy for patients with metastatic castration-resistant prostate cancer. Uro-Today. On-line, June 29, 2021.

62. Yu EY. From the Desk of Evan Yu: Abscopal effect for prostate cancer? Does this really hold promise? Uro-Today. On-line, August 2, 2021.

63. Yu EY. From the Desk of Evan Yu: Prostate-specific membrane antigen (PSMA) PET for initial staging of prostate cancer – now that it's regulatory approved, what's next? Uro-Today. On-line, September 1, 2021.

64. Yu EY. From the Desk of Evan Yu: Maintenance therapy and beyond with avelumab. Uro-Today. On-line, September 28, 2021.

65. Yu EY. From the Desk of Evan Yu: Upper tract urothelial carcinoma – a patient population that deserves more attention in clinical trials. Uro-Today. On-line, November 8, 2021.

66. Yu EY. From the Desk of Evan Yu: Metastatic castration-sensitive prostate cancer, the advances keep coming with chemohormonal therapy. Uro-Today. On-line, November 30, 2021.

67. Yu EY. From the Desk of Evan Yu: Combination strategies with PD-1/PD-L1 inhibition for patients with metastatic castration-sensitive prostate cancer. Uro-Today. On-line, January 3, 2022.

68. Yu EY. From the Desk of Evan Yu: Can PARP inhibitors make it into the metastatic castration-sensitive prostate cancer disease state? Uro-Today. On-line, February 1, 2022.

69. Yu EY. From the Desk of Evan Yu: Triple combination therapy with chemohormonal approaches: Paving a path forward in various disease states with newer agents and even more treatment intensification. Uro-Today. On-line, March 3, 2022.

70. Yu EY. From the Desk of Evan Yu: Pembrolizumab and beyond for BCG-unresponsive, high-risk, non-muscle invasive bladder cancer. Uro-Today. On-line, April 1, 2022.

71. Yu EY. From the Desk of Evan Yu: High-risk, non-muscle invasive bladder cancer – is there anything we should be adding to BCG? Uro-Today. On-line, May 1, 2022.

72. Yu EY. From the Desk of Evan Yu: Prostate cancer aggressive variants deserve clinical trial attention. Uro-Today. On-line, June 3, 2022.

73. Yu EY. From the Desk of Evan Yu: Are there any other PARP Inhibitor combinations in prostate cancer we should be exploring? Uro-Today. On-line, June 30, 2022.

74. Yu EY. From the Desk of Evan Yu: Even with new treatment advances for metastatic castration-sensitive prostate cancer, there is still opportunity to bring in radiopharmaceutical therapy. Uro-Today. On-line, August 15, 2022.

75. Yu EY. From the Desk of Evan Yu: Relugolix is available, but additional clinical trial investigation is ongoing. Uro-Today. On-line, September 6, 2022.

76. Yu EY. From the Desk of Evan Yu: Cisplatinum-ineligible patients with muscle-invasive localized urothelial carcinoma still do not have good systemic therapy options for neoadjuvant treatment. Uro-Today. On-line, September 28, 2022.

77. Yu EY. From the Desk of Evan Yu: Refractory testicular germ cell tumors – where should we go next? Uro-Today. On-line, October 31, 2022.

78. Yu EY. From the Desk of Evan Yu: Is there synergism when combining antibody drug conjugates and immune-oncology agents for urothelial carcinoma? Uro-Today. On-line, November 30, 2022.

79. Yu EY. From the Desk of Evan Yu: Third or fourth place in the race? No problem – the case for more trials using darolutamide for patients with prostate cancer. Uro-Today. On-line, January 3, 2023.

ABSTRACTS (LAST 5 YEARS)

1. Montgomery RB, Russell KJ, Liao JJ, Ellis WJ, Cheng HH, Yu EY, Mostaghel EA. A phase II study of degarelix prior to radiation on prostatic tissue androgens. *J Clin Oncol* 36, 2018 (suppl 6S; abstr 103). Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2018.

2. Lim DM, Gulati R, Aleshin-Guendel S, Cheng HH, Gawne AM, Wingate JT, Etzioni RD, Yu EY. Proportion of biochemically-recurrent prostate cancer patients with durable undetectable PSA after short-course androgen deprivation therapy. *J Clin Oncol* 36, 2018 (suppl 6S; abstr 207). Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2018.

3. Necchi A, Mariani L, Lo Vullo S, Raggi D, Giannatempo P, Bamias A, Crabb SJ, Bellmunt J, Yu EY, Niegisch G, Vaishampayan UN, Theodore C, Berthold DR, Srinivas S, Sridhar SS, Plimack ER, Rosenberg JE, Powles T, Galsky M, Sonpavde G. Impact of number of cycles of platinum-based first-line chemotherapy for advanced urothelial carcinoma. *J Clin Oncol* 36, 2018 (suppl 6S; abstr 426). Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2018.

4. Necchi A, Pond GR, Plimack ER, Niegisch G, Yu EY, Pal SK, Bamias A, Agarwal N, Alva AS, Srinivas S, Crabb SJ, Vaishampayan UN, Bowles DW, Berthold DR, Theodore C, Sridhar SS, Powles T, Rosenberg JE, Bellmunt J, Galsky MD, Retrospective International Study of Invasive/Advanced Cancer of the Urothelium (RISC). Nomogram-based risk prediction of local and distant relapse after radical cystectomy, and role of perioperative chemotherapy, in patients with muscle-invasive bladder cancer: A multicenter study. *J Clin Oncol* 36, 2018 (suppl 6S; abstr 448). Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2018.

5. Raggi D, Pond G, Giannatempo P, Plimack ER, Niegisch G, Yu EY, Pal SK, Bamias A, Agarwal N, Alva AS, Ladoire S, Srinivas S, Crabb SJ, Baniel J, Vaishampayan UN, Bowles DW, Berthold DR,

Theodore C, Sridhar SS, Powles T, Rosenberg JE, Bellmunt J, Galsky MD, Necchi A, Retrospective International Study of Invasive/Advanced Cancer of the Urothelium (RISC). Nomogram-based risk prediction of local and distant relapse after radical cystectomy, and role of perioperative chemotherapy, in patients with muscle-invasive bladder cancer: A multicenter study. Abstract 368, 2018. Poster presentation at *33rd Annual European Association of Urology Congress*, Copenhagen, Denmark, Mar. 2018.

6. Winters B, Holt S, Wright J, Brisbane W, Ramos JD, Yu EY, Schade G. Metformin use in diabetic Medicare beneficiaries is associated with improved survival following radical cystectomy. Abstract MP71-07, 2018. 2018 Annual Meeting of the American Urological Association Education and Research, Inc., San Francisco, CA, May 2018.

7. Inman B, Vu T, Yu EY, Haynes H, Sheikh NA, George D. Real time imaging demonstrating T-cell mediated destruction of prostatic acid phosphatase-expressing cells in patients treated with sipuleucek-T. Abstract PD14-07, 2018. 2018 Annual Meeting of the American Urological Association Education and Research, Inc., San Francisco, CA, May 2018.

8. Schweizer MT, Antonarakis ES, Bismar TA, Guedes L, Cheng HH, Tretiakova MS, Vakar-Lopez F, Klemfuss N, Konnick EQ, Mostaghel EA, Hsieh AC, Nelson PS, Yu EY, Montgomery RB, True LD, Epstein JI, Lotan TL, Pritchard C. Genomic characterization of ductal adenocarcinoma of the prostate. *J Clin Oncol* 36, 2018 (suppl; abstr 5030). Poster presentation at ASCO Annual Meeting, Chicago, IL, Jun. 2018.

9. Caffo O, Wissing M, Bianchini D, Bergman AM, Birkeba F, Thomsen K, Schmid S, Yu EY, Bournakis E, Sella A, Basso U, De Giorgi U, Tucci M, Gelderblom H, Galli L, Sperduti I, Oudard S, CASTOR Study Investigators. Survival outcomes from a cumulative analysis from worldwide observational studies on sequential use of new agents in metastatic castration-resistant prostate cancer (CASTOR study). *J Clin Oncol* 36, 2018 (suppl; abstr 5026). Poster presentation at ASCO Annual Meeting, Chicago, IL, Jun. 2018.

10. De Wit R, Powles T, Castellano DE, Necchi A, Lee JL, Van der Heijden MS, Matsubara N, Bamias A, Flechon A, Sternberg CN, Drakaki A, Yu EY, Hamid O, Zimmermann A, Gao L, Long A, Walgren RA, Bell-McGuinn KM, Petrylak DP. Ramucirumab exposure-response relationship in RANGE, a randomized phase III trial of docetaxel with or without ramucirumab in advanced urothelial carcinoma patients who progressed on or after platinum therapy. *J Clin Oncol* 36, 2018 (suppl; abstr 4526). Poster presentation at ASCO Annual Meeting, Chicago, IL, Jun. 2018.

11. Bandini M, Briganti A, Plimack ER, Niegisch G, Yu EY, Bamias A, Agarwal N, Sridhar SS, Sternberg CN, Vaishampayan UN, Theodore C, Rosenberg JE, Bellmunt J, Galsky MD, Montorsi F, Necchi A. Relapse-free survival of clinical T2-4N0 urothelial bladder carcinoma after radical cystectomy, with or without perioperative chemotherapy: Endpoints for clinical trial design. *J Clin Oncol* 36, 2018 (suppl; abstr 4535). Poster presentation at ASCO Annual Meeting, Chicago, IL, Jun. 2018.

12. Yu EY, Gulati R, Aleshin-Guendel S, Cheng HH, Gawne AM, Wingate JT, Etzioni RD, Lim DM. Association of undetectable PSA with time to metastasis and survival after short-course androgen deprivation therapy for biochemically-recurrent prostate cancer patients. *J Clin Oncol* 36, 2018 (suppl; abstr e17073). ASCO Annual Meeting, Chicago, IL, Jun. 2018.

13. Muzi M, O'Sullivan F, Muzi JP, Mankoff DA, Yu EY. Whole body ^{18}F-fluoride PET SUV imaging to monitor response to dasatinib therapy in castration-resistant prostate cancer bone metastases: Secondary results from ACRIN 6687. Journal of Nuclear Medicine 59:1504. 2018. Poster presentation at Society of Nuclear Medicine and Molecular Imaging Annual Meeting, Philadelphia, PA, Jun. 2018.

14. Petrylak DP, Sternberg CN, Drakaki A, de Wit R, Nishiyama H, Necchi A, Castellano D, Bamias A, Chi KN, van der Heijden MS, Matsubara N, Hussain S, Flechon A, Alekseev BY, Yu EY, Walgren RA, Fusso F, Zimmermann AH, Bell-Mcguinn KM, Powles TB. RANGE, a phase III, randomized, placebo-controlled, double-blind trial of ramucirumab and docetaxel in platinum-refractory urothelial carcinoma: Overall survival results. *Ann Oncol* 29(8), 1 Oct. 2018, mdy283.071. Abstract 865PD. Oral presentation at 2018 *43rd ESMO European Cancer Congress*, Munich, Germany, Oct. 2018.

15. Almeida DVP, de Oliveira CZ, Mariano RC, Kater FER, Souza MCLA, Ruiz-Schutz VC, Yamamura R, Saraiva De Carvalho R, Maluf FC, Morgans AK, Srinivas S, Gupta S, Dorff T, Yu EY, Schutz FA. Non-metastatic castration-resistant prostate cancer: Meta-analysis of efficacy and safety with novel hormonal agents apalutamide and enzalutamide. *Ann Oncol* 29(8), 1 Oct. 2018, mdy284.017. Abstract 808P. Poster presentation at 2018 *43rd ESMO European Cancer Congress*, Munich, Germany, Oct. 2018.

16. Pachynski R, Harshman L, Appleman L, Monk P, Bitting R, Kucuk O, Millard F, Seigna J, Fling S, Ramchurren N, Hess B, D'Amico L, Lacroix A, Kaiser J, Morre M, Gregoire A, Cheever M, Yu EY. T cell response induced by the addition of IL-7 treatment following sipuleucel-T immunotherapy in metastatic castration resistant prostate cancer. Abstract P298, 2018. Poster presentation at 2018 *Society for Immunotherapy of Cancer 33rd Annual Meeting*, Washington, DC, Nov. 2018.

17. Markowski MC, Eisenberger MA, Antonarakis ES, Yu EY, Barnette G, Rodriguez D, Getzenberg RH, Steiner MS. Design of phase 1b/II study of oral VERU-111, an α and β-tubulin inhibitor, for the treatment of metastatic castration- and androgen-blocking-agent-resistant prostate cancer. *J Clin Oncol* 37, 2019 (suppl 7S; abstr TPS330). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2019.

18. Winters B, De Sarkar N, Arora S, Bolouri H, Vakar-Lopez F, Cheng HH, Yu EY, Kollath L, Grivas P, McFerrin L, Montgomery RB, Wright JL, Lam HM, Hsieh AC. Distinct genomic hallmarks exist between metastatic upper and lower tract urothelial cancer. *J Clin Oncol* 37, 2019 (suppl 7S; abstr 371). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2019.

19. Nyame YA, Holt SK, Winters B, Psutka SP, Dash A, Schade GR, Lin DW, Yu EY, Gore JL, Wright JL. Neoadjuvant chemotherapy utilization in muscle-invasive bladder cancer: Increasing yet inappropriate use? *J Clin Oncol* 37, 2019 (suppl 7S; abstr 441). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2019.

20. De Wit R, Powles T, Castellano DE, Necchi A, Lee JL, Van der Heijden MS, Matsubara N, Bamias A, Flechon A, Sternberg CN, Drakaki A, Yu EY, Hamid O, Zimmermann AH, Gao L, Long A, Walgren RA, Bell-McGuinn KM, Petrylak DP. Ramucirumab exposure-response relationship in RANGE: A randomized phase III trial of ramucirumab plust docetaxel versus placebo plus docetaxel in advanced platinum-refractory urothelial carcinoma patients. *J Clin Oncol* 37,

2019 (suppl 7S; abstr 353). Oral presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2019.

21. **Yu EY, Massard C, Retz M, Tafreshi A, Galceran JC, Hammerer P, Fong PCC, Shore N, Joshua A, Linch MD, Gurney H, Romano E, Augustin M, Piulats JM, Wu H, Schloss C, Poehlein CH, De Bono JS. KEYNOTE-365 Cohort A: Pembrolizumab plus olaparib in docetaxel-pretreated patients with metastatic castrate-resistant prostate cancer. *J Clin Oncol* 37, 2019 (suppl 7S; abstr 145). Oral presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2019.**

22. Sonpavde G, Maughan BL, Wei XX, McGregor BA, Kilbridge KL, Lee RJ, Yu EY, Schweizer MT, Montgomery RB, Cheng HH, Hsieh AC, Birhiray RE, Gabrail NY, Nemunaitis JJ, Rezazadeh A, Van Veldhuizen PJ, Vogelzang NJ, Heery CR, Grivas P. A phase II, multicenter, single-arm trial of CV301 plus atezolizumab in locally advanced (unresectable) or metastatic urothelial cancer. *J Clin Oncol* 37, 2019 (suppl 7S; abstr TPS494). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2019.

23. Smith MR, Sandhu SK, Kelly WK, Scher HI, Efstathiou E, Lara P, Yu EY, George DJ, Chi KN, Summa J, Kothari N, Zhao X, Espina BM, Ricci DS, Simon JS, Tran N, Fizazi K, GALAHAD Investigators. Phase II study of niraparib in patients with metastastic castration-resistant prostate cancer and biallelic DNA-repair gene defects: Preliminary results of GALAHAD. *J Clin Oncol* 37, 2019 (suppl 7S; abstr 202). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2019.

24. Massard C, Retz M, Hammerer P, Quevedo F, Fong PCC, Berry WR, Gurnery H, Piulats JM, Joshua A, Linch MD, Kolinsky M, Romano E, Sridhar SS, Conter HJ, Augustin M, Wu, H, Schloss C, Poehlein CH, Yu EY. KEYNOTE-365 Cohort B: Pembrolizumab plus docetaxel and prednisone in abiraterone or enzalutamide-pretreated patients with metastatic castration-resistant prostate cancer. *J Clin Oncol* 37, 2019 (suppl 7S; abstr 170). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2019.

25. Fong PCC, Retz M, Drakaki A, Massard C, Berry WR, Romano E, Bono JS, Feyerabend S, Appleman LJ, Conter HJ, Sridhar SS, Shore ND, Linch MD, Joshua A, Gurney H, Wu, H, Schloss C, Poehlein CH, Yu EY. KEYNOTE-365 Cohort C: Pembrolizumab plus enzalutamide in abiraterone-pretreated patients with metastatic castration-resistant prostate cancer. *J Clin Oncol* 37, 2019 (suppl 7S; abstr 171). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2019.

26. Petrylak DP, Balar AV, O'Donnell PH, McGregor BA, Heath EI, Yu EY, Galsky MD, Hahn NM, Gartner EM, Pinelli J, Melhem-Bertrandt A, Rosenberg JE. EV-201: Results of enfortumab vedotin monotherapy for locally advanced or metastatic urothelial cancer previously treated with platinum and immune checkpoint inhibitors. *J Clin Oncol* 37, 2019 (suppl; abstr LBA4505). Oral presentation at ASCO Annual Meeting, Chicago, IL, Jun. 2019.

27. Yu EY, Massard C, Retz M, Tafreshi A, Carles J, Hammerer P, Fong PCC, Shore N, Joshua AM, Linch MD, Gurney H, Romano E, Augustin M, Piulats JM, Wu H, Schloss C, Poehlein CH, De Bono JS. Pembrolizumab plus olaparib in docetaxel-pretreated patients with metastatic castrate-resistant prostate cancer: Cohort A of the phase 1b/2 KEYNOTE-365 study. *J Clin Oncol* 37, 2019 (suppl; abstr 5027). Poster presentation at ASCO Annual Meeting, Chicago, IL, Jun. 2019.

28. Nyame YA, Holt SK, Winters B, Psutka SP, Dash A, Schade GR, Lin DW, Diamantopoulos LN, Grivas P, Yu EY, Gore JL, Wright JL. Increasing use of neoadjuvant chemotherapy in muscle-invasive bladder cancer: Prognostic impact of non-standard of care regimens. *J Clin Oncol* 37, 2019 (suppl; abstr 4532). Poster presentation at ASCO Annual Meeting, Chicago, IL, Jun. 2019.

29. Khaki AR, Diamantopoulos LN, Devitt ME, Drakaki A, Shreck E, Joshi M, Velho PI, Alonso L, Nelson AA, Liu S, Moses MW, Barata PC, Hoimes CJ, Galsky MD, Sonpavde G, Yu EY, Shankaran V, Lyman GH, Grivas P. Outcomes of patients with metastatic urothelial cancer and poor performance status receiving anti-PD(L)1 agents. *J Clin Oncol* 37, 2019 (suppl; abstr 4525). Poster presentation at ASCO Annual Meeting, Chicago, IL, Jun. 2019.

30. Winters B, Diamantopoulos LN, Tretiakova MS, True LD, Lee JH, Zeng J, Liao J, Cheng HH, Schweizer MT, Hsieh AC, Yu EY, Schade GR, Gore JL, Lin DW, Dighe M, Vakar-Lopez F, Russell JR, Grivas P, Montgomery RB, Wright JL. Bladder Cancer Multidisciplinary Clinic model: Impact on imaging, pathology and treatment recommendations. *J Clin Oncol* 37, 2019 (suppl; abstr 4537). Poster presentation at ASCO Annual Meeting, Chicago, IL, Jun. 2019.

31. Bandini M, Pederzoli F, Madison R, Briganti A, Plimack ER, Ross JS, Niegisch G, Yu EY, Bamias A, Agarwal N, Sridhar SS, Rosenberg JE, Bellmunt J, Galsky MD, Gallina A, Salonia A, Montorsi F, Ali SM, Chung J, Necchi A. Squamous cell variant histology in muscle-invasive bladder cancer: A comprehensive clinical, genomic, and therapeutic assessment from multiple datasets. *J Clin Oncol* 37, 2019 (suppl; abstr 4535). Poster presentation at ASCO Annual Meeting, Chicago, IL, Jun. 2019.

32. Yu EY, Fling S, Salim B, Sweis RF, Chatta GS, Jain RK, Delacroix SE, Moon H, Lacroix A, Kaiser JC, Sharon E, Cheever MA, Pachynski R. A randomized phase II study of atezolizumab plus recombinant human IL-7 (CYT107) or atezolizumab alone in patients with locally advanced or metastatic urothelial carcinoma: A Cancer Immunotherapy Trials Network trial (CITN-14). *J Clin Oncol* 37, 2019 (suppl; abstr TPS4586). Poster presentation at ASCO Annual Meeting, Chicago, IL, Jun. 2019.

33. Fong PCC, Retz M, Drakaki A, Massard C, Berry WR, Romano E, Bono JS, Feyerabend S, Appleman LJ, Conter HJ, Sridhar SS, Shore ND, Linch MD, Joshua A, Gurney H, Wu, H, Schloss C, Poehlein CH, Yu EY. Pembrolizumab plus enzalutamide in abiraterone-pretreated patients with metastatic castration-resistant prostate cancer: Cohort C of the phase 1b/2 KEYNOTE-365 study. *J Clin Oncol* 37, 2019 (suppl; abstr 5010). **Poster Discussion Session at ASCO Annual Meeting, Chicago, IL, Jun. 2019.**

34. Graham L, Reder N, Gulati R, Grivas P, Wright JL, Yu EY, Hou W, Nega K, Yezefski T, Montgomery RB, Mostaghel EA, Ellis WJ, True LD, Lin DW, Nelson PS, Schweizer MT. Targeting backdoor androgen synthesis through AKR1C3 inhibition, A presurgical hormonal ablative trial in high risk localized prostate cancer. *J Clin Oncol* 37, 2019 (suppl; abstr 5081). Poster presentation at ASCO Annual Meeting, Chicago, IL, Jun. 2019.

35. Massard C, Retz M, Hammerer P, Quevedo F, Fong PCC, Berry WR, Gurnery H, Piulats JM, Joshua A, Linch MD, Kolinsky M, Romano E, Sridhar SS, Conter HJ, Augustin M, Wu, H, Schloss C, Poehlein CH, Yu EY. Pembrolizumab plus docetaxel and prednisone in abiraterone or enzalutamide-pretreated patients with metastatic castration-resistant prostate cancer: Cohort

B of the phase 1b/2 KEYNOTE-365 study. *J Clin Oncol* 37, 2019 (suppl; abstr 5029). Poster presentation at ASCO Annual Meeting, Chicago, IL, Jun. 2019.

36. Grunewald CM, Henn A, Galsky MD, Plimack ER, Harshman LC, Yu EY, Crabb SJ, Pal SK, Alva AS, Powles T, De Giorgi U, Agarwal N, Bamias A, Ladoire S, Necchi A, Vaishampayan UN, Sternberg CN, Bellmunt J, Baniel J, Niegisch G. Impact of timing of adjuvant chemotherapy following radical cystectomy for bladder cancer on patient survival. *J Clin Oncol* 37, 2019 (suppl; abstr e16017). ASCO Annual Meeting, Chicago, IL, Jun. 2019.

37. Diamantopoulos LN, Khaki AR, Vakar-Lopez F, Tretiakova MS, Gore JL, Schade GR, Psutka SP, Hsieh AC, Lee JK, Yezefski T, Schweizer MT, Cheng HH, Yu EY, Grivas P, Montgomery RB, Wright JL. Patient characteristics, treatment patterns, outcomes and prognostic factors in plasmacytoid urothelial carcinoma. *J Clin Oncol* 37, 2019 (suppl; abstr e16007). ASCO Annual Meeting, Chicago, IL, Jun. 2019.

38. Yu EY, Lu X, Kim J, Antonarakis ES. KEYLYNK-010: Phase 3 study of pembrolizumab plus olaparib vs. enzalutamide or abiraterone in enzalutanmide- or abiraterone-pretreated patients with metastatic castration-resistant prostate cancer who had progression on chemotherapy. *ESMO Congress* Abstract 893TIP, 2019 European Society of Medical Oncology Congress. Barcelona, Spain, Sept. 2019. Poster presentation at ESMO Congress, Barcelona, Spain, Sept. 2019.

39. Smith MR, Sandhu S, Kelly WK, Scher HI, Efstathiou E, Lara P, Yu EY, George DJ, Chi KN, Saad F, Summa J, Freedman JM, Mason GE, Zhu E, Ricci DS, Simon JS, Cheng S, Fizazi K. Pre-specified interim analysis of GALAHAD: A phase 2 study of niraparib in patients with metastatic castration-resistant prostate cancer and biallelic DNA-repair gene defects. *ESMO Congress* Abstract LBA50, 2019 European Society of Medical Oncology Congress. Barcelona, Spain, Sept. 2019. Poster presentation at ESMO Congress, Barcelona, Spain, Sept. 2019.

40. McGregor BA, O'Donnell PH, Balar A, Petrylak D, Rosenberg JE, Yu EY, Quinn DI, Shah S, Pinelli J, Hepp Z, Galsky MD. Quality of life of metastatic urothelial cancer patients treated with enfortumab vedotin following platinum-containing chemotherapy and anti-programmed death 1 or anti-programmed death-ligand 1 (PD-1/L1) therapy: Data from EV-201 cohort 1. *ESMO Congress* Abstract 921P, 2019 European Society of Medical Oncology Congress. Barcelona, Spain, Sept. 2019. Poster presentation at ESMO Congress, Barcelona, Spain, Sept. 2019.

41. Appleman LJ, Piulats J, Mar N, Arranz JA, Joshua A, Mayer TM, Shore N, Wu H, Schloss C, Yu EY. KEYNOTE 365 Cohort D: Phase 1b/2 study of pembrolizumab plus abiraterone acetate and prednisone in metastatic castration-resistant prostate cancer. *Journal for ImmunoTherapy of Cancer* Nov. 26 Suppl P382. Poster presentation at 2019 Society for Immunotherapy of Cancer at National Harbor, MD, Nov. 2019.

42. Yu EY, Park SH, Huang YH, Bennamoun M, Xu L, Kim J, Antonarakis EA. Pembrolizumab plus olaparib vs. enzalutamide or abiraterone in patients with metastatic castration-resistant prostate cancer who experienced progression on chemotherapy: Phase 3 KEYLYNK-010 study. *Journal for ImmunoTherapy of Cancer* Nov. 26 Suppl P390. Poster presentation at 2019 Society for Immunotherapy of Cancer at National Harbor, MD, Nov. 2019.

43. Graham L, Montgomery RB, Cheng HH, Yu EY, Alva AS, Schweizer MT. Mismatch repair deficiency in metastatic prostate cancer. *J Clin Oncol* 38, 2020 (suppl 6; abstr 194). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2020.

44. Carlson AS, Acevedo R, Lim DM, Gulati R, Yu EY, Schweizer MT. Impact of DNA damage repair mutations on treatment outcomes in men receiving conventional therapy for metastatic castration resistant prostate cancer. *J Clin Oncol* 38, 2020 (suppl 6; abstr 172). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2020.

45. Yu EY, Laidley D, Pouliot F, Probst S, Saad F, Sabbagh R, Sartor AO. A multicenter, randomized, controlled phase II study: Efficacy and safety of PSMA-targeted radioligand therapy ^{131}I-1095 plus enzalutamide in ^{18}F-DCFPyL PSMA scan avid, metastatic castration-resistant prostate cancer patients post-abiraterone progression (ARROW). *J Clin Oncol* 38, 2020 (suppl 6; abstr TPS260). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2020.

46. Graff JN, Cheng HH, Vuky J, Alumkal JJ, Kreitner D, Petreaca D, Grivas P, Schweizer MT, Higano CS, Chen Y, Yu EY, Beer TM. Phase II study of cabazitaxel plus enzalutamide in metastatic castration-resistant prostate cancer. *J Clin Oncol* 38, 2020 (suppl 6; abstr 86). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2020.

47. Miller NJ, Khaki AR, Diamantopoulos LN, Bilen MA, Santos VS, Morales-Barrera R, Devitt ME, Nelson AA, Shreck E, Assi H, Rodriguez-Vida A, Lythgoe M, Drakaki A, Joshi M, Velho PI, Moses MW, Galsky MD, Sonpavde G, Yu EY, Grivas P. Histologic subtype and response to immune checkpoint inhibitor therapy in advanced urothelial cancer. *J Clin Oncol* 38, 2020 (suppl 6; abstr 495). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2020.

48. Sokolova A, Marshall CH, Lozano R, Grivas P, Higano CS, Lotan TL, Montgomery RB, Nelson P, Olmos D, Schweizer MT, Yezefski T, Yu EY, Paller CJ, Castro E, Antonarakis ES, Cheng HH. Treatment response comparisons between *ATM* and *BRCA2* germline carriers for metastatic castration resistant prostate cancer. *J Clin Oncol* 38, 2020 (suppl 6; abstr 63). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2020.

49. Smith MR, Fizazi K, Sandhu SK, Kelly WK, Efstathiou E, Lara P, Yu EY, George DJ, Chi KN, Saad F, Summa J, Freedman JM, Mason G, Espina BM, Zhu E, Ricci DS, Snyder LA, Simon JS, Cheng S, Scher HI. Niraparib in patients with metastatic castration-resistant prostate cancer and biallelic DNA-repair gene defects: Correlative measures of tumor response in phase II GALAHAD study. *J Clin Oncol* 38, 2020 (suppl 6; abstr 118). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2020.

50. Cheng HH, DeJong M, Yu EY, Gulati R, Rettig M, Higano CS, Nelson P, Pritchard CC, Montgomery RB. A pilot study of docetaxel and carboplatin for treatment of patients with metastatic castration resistant prostate cancer containing biallelic inactivation of genes in the *BRCA1/2* pathway. *J Clin Oncol* 38, 2020 (suppl 6; abstr 127). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2020.

51. Yu EY, Park SH, Huang YH, Bennamoun M, Xu L, Kim J, Antonarakis ES. Phase III study of pembrolizumab plus olaparib versus enzalutamide or abiraterone acetate in patients with metastatic castration-resistant prostate cancer who progressed on chemotherapy: KEYLYNK-

010. *J Clin Oncol* 38, 2020 (suppl 6; abstr TPS256). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2020.

52. Wong RL, Duong MT, Tangen C, Agarwal N, Cheng HH, Vogelzang NJ, Hussain M, Thompson IM, Quinn DI, Yu EY. Survival outcomes and risk group validation from SWOG S0925, a randomized phase II study of androgen deprivation +/- cixutumumab, in new metastatic hormone-sensitive prostate cancer. *J Clin Oncol* 38, 2020 (suppl 6; abstr 106). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2020.

53. Diamantopoulos LN, Khaki AR, Gadzinski AJ, Winters B, Vakar-Lopez F, Tretiakova MS, Gore JL, Schade GR, Psutka SP, Hsieh AC, Lee JK, Yezefski T, Schweizer MT, Cheng HH, Yu EY, Lin DW, Montgomery RB, Grivas P, Wright JL. Micropapillary urothelial carcinoma: A comparative analysis of oncologic outcomes compared to conventional urothelial carcinoma. *J Clin Oncol* 38, 2020 (suppl 6; abstr 459). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2020.

54. Yu EY, Piulats JM, Gravis G, Laguerre B, Arija JAA, Oudard S, Fong PCC, Kolinsky MP, Augustin M, Feyerabend S, Kam AE, Gurney H, Tafreshi A, Retz M, Berry WR, Mar N, Wu H, Schloss C, Poehlein CH, De Bono JS. KEYNOTE-365 cohort A updated results: Pembrolizumab plus olaparib in docetaxel-pretreated patients with metastatic castration-resistant prostate cancer. *J Clin Oncol* 38, 2020 (suppl 6; abstr 100). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2020.

55. Berry WR, Fong PCC, Piulats JM, Appleman LJ, Conter HJ, Feyerabend S, Shore ND, Gravis G, Laguerre B, Gurney H, Retz M, Romano E, Mourey L, De Bono JS, Kam AE, Emmenegger U, Wu H, Schloss C, Poehlein CH, Yu EY. KEYNOTE-365 cohort C updated results: Pembrolizumab plus enzalutamide in abiraterone-pretreated patients with metastatic castrate-resistant prostate cancer. *J Clin Oncol* 38, 2020 (suppl 6; abstr 102). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2020.

56. Kolinsky MP, Gravis GG, Piulats JM, Sridhar SS, Romano E, Berry WR, Gurney H, Retz M, Appleman LJ, Boegemann M, De Bono JS, Joshua AM, Emmenegger U, Conter HJ, Laguerre B, Wu H, Schloss C, Poehlein CH, Yu EY. KEYNOTE-365 cohort B updated results: Pembrolizumab plus docetaxel and prednisone in abiraterone or enzalutamide-pretreated patients with metastatic castrate-resistant prostate cancer. *J Clin Oncol* 38, 2020 (suppl 6; abstr 103). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2020.

57. Yu EY, Fong P, Piulats JM, Appleman L, Feyerabend S, Shore N, Gravis G, Laguerre B, Retz M, Romano E, Mourey L, de Bono JS, Kam A, Emmenegger U, Wu H, Schloss C, Poehlein C, Berry W. Pembrolizumab plus enzalutamide in abiraterone-pretreated patients with metastatic castration-resistant prostate cancer: Updated results from KEYNOTE-365 cohort C. Abstract PD16-12, 2020. Oral (virtual) presentation at the 2020 Annual Meeting of the American Urological Association Education and Research, Inc., Washington, DC, May 2020.

58. Soria F, Black PC, Fairey AS, Cookson MS, Yu EY, Kassouf W, Dall'Era MA, Sridhar SS, McGrath JS, Wright JL, Thorpe AC, Morgan TM, Holzbeierlein JM, Bivalacqua TJ, North S, Barocas DA, Lotan Y, Grivas P, Stephenson AJ, Shah JB, Van Rhijn BW, Spiess PE, Sharait SF, Gontero P. Neoadjuvant chemotherapy plus radical cystectomy versus radical cystectomy alone in clinical T2 bladder cancer patients without hydronephrosis: Results from a large multicenter cohort

study. Abstract PD60-05. Presentation at the 2020 Annual Meeting of the American Urological Association Education and Research, Inc., Washington, DC, May 2020.

59. Yu EY, Laidley D, Pouliot F, Probst S, Sabbagh R, Esposito G, Saad F, Sartor AO. A multicenter, randomized, controlled phase II study: Efficacy and safety of PSMA-targeted radioligand therapy ^{131}I-1095 plus enzalutamide in ^{18}F-DCFPyL PSMA scan avid, metastatic castration-resistant prostate cancer patients post-abiraterone progression (ARROW). *J Clin Oncol* 38: 2020 (suppl; abstr TPS5596). Poster presentation at 2020 ASCO Virtual Scientific Program, May 2020.

60. Yu EY, Pieczonka CM, Briganti A, Murphy DG, Thierry L, Luz M, Suzuki H, Thiery-Vuillemin A, Ortiz JA, Guan R, Armstrong AJ. DAROL: DARolutamide ObservationaL study patients in nonmetastatic castration-resistant prostate cancer patients. *J Clin Oncol* 38: 2020 (suppl; abstr TPS5593). Poster presentation at 2020 ASCO Virtual Scientific Program, May 2020.

61. Kelly WK, Danila DC, Edenfield WJ, Aggarwal RR, Petrylak DP, Sartor AO, Sumey CJ, Dorff TB, Yu EY, Adra N, Waterhouse DM, Armstrong AJ, Horvath L, Pook DW, Appleman LJ, Lau A, Salvati M, Kouros-Mehr H. Phase I study of AMG 509, a STEAP1 X CD3 T cell-recruiting XmAb 2+1 immune therapy, in patients with metastatic castration-resistant prostate cancer. *J Clin Oncol* 38: 2020 (suppl; abstr TPS5589). Poster presentation at 2020 ASCO Virtual Scientific Program, May 2020.

62. Sridhar SS, Kolinsky MP, Gravis G, Mourey L, Piulats Rodriguez JMM, Romano E, Berry WR, Gurney H, Retz M, Appleman LJ, Boegemann M, De Bono JS, Joshua AM, Emmenegger U, Conter HJ, Laguerre B, Wu H, Qiu P, Schloss C, Yu EY. Pembrolizumab plus docetaxel and prednisone in patients with abiraterone acetate or enzalutamide-pretreated metastatic castration-resistant prostate cancer: KEYNOTE-365 cohort B efficacy, safety, and biomarker results. *J Clin Oncol* 38: 2020 (suppl; abstr 5550). Poster presentation at 2020 ASCO Virtual Scientific Program, May 2020.

63. Yu EY, Piulats Rodrigeuz JMM, Gravis G, Laguerre B, Arija JAA, Oudard S, Fong PCC, Kolinsky MP, Augustin M, Todenhofer T, Kam AE, Gurney H, Tafreshi A, Retz M, Berry WR, Mar N, Wu H, Qiu P, Schloss C, De Bono JS. Pembrolizumab plus olaparib in patients with docetaxel-pretreated metastatic castration resistant prostate cancer: KEYNOTE-365 cohort A efficacy, safety, and biomarker results. *J Clin Oncol* 38: 2020 (suppl; abstr 5544). Poster presentation at 2020 ASCO Virtual Scientific Program, May 2020.

64. Conter HJ, Shore ND, Berry WR, Fong PCC, Piulats Rodriguez JMM, Appleman LJ, Todenhofer T, Gravis G, Laguerre B, Gurney H, Retz M, Romano E, Mourey L, De Bono JS, Kam AE, Emmenegger U, Wu H, Qiu P, Schloss C, Yu EY. Pembrolizumab plus enzalutamide in patients with abiraterone acetate-pretreated metastatic castration-resistant prostate cancer: KEYNOTE 365 cohort C efficacy, safety, and biomarker results. *J Clin Oncol* 38: 2020 (suppl; abstr 5545). Poster presentation at 2020 ASCO Virtual Scientific Program, May 2020.

65. Do OA, Ferris L, Holt SK, Ramos J, Harshman LC, Plimack ER, Crabb SJ, Pal SK, De Giorgi U, Ladoire S, Baniel J, Necchi A, Vaishampayan UN, Golshayan AR, Bamias A, Bellmunt J, Srinivas S, Dorff TB, Galsky MD, Yu EY. Treatment of metastatic recurrence of urothelial carcinoma after previous cisplatin-based chemotherapy: A retrospective comparison of different chemotherapy regimens. *J Clin Oncol* 38: 2020 (suppl; abstr e17005).

66. Ngo S, Diamantopoulos LN, Maldonado R, O'Malley RB, Laidlaw G, Fintelmann FJ, Holt SK, Gore JL, Schade GR, Lin DW, Grivas P, Montgomery RB, Hsieh AC, Cheng HH, Yezefski T, Schweizer MT, Yu EY, Wright JL, Psutka SP. Skeletal muscle index and adverse events during a bladder cancer treatment episode. *J Clin Oncol* 38: 2020 (suppl; abstr e17016).

67. Diamantopoulos LN, Sekar RR, Khaki AR, Miller N, Gadzinski AJ, Psutka SP, Gore JL, Schade GR, Lin DW, Tretiakova MS, Vakar-Lopez F, True LD, Hsieh AC, Cheng HH, Yu EY, Schweizer MT, Yezefski T, Montgomery RB, Grivas P, Wright JL. Perioperative blood transfusion and postoperative outcomes in patients undergoing radical cystectomy for bladder cancer. *J Clin Oncol* 38: 2020 (suppl; abstr e17012).

68. Sekar RR, Diamantopoulos LN, Khaki AR, Vakar-Lopez F, Tretiakova MS, Psutka SP, Holt SK, Gore JL, Schade GR, Lin DW, Hsieh AC, Lee JK, Yezefski T, Schweizer MT, Cheng HH, Yu EY, True LD, Montgomery RB, Grivas P, Wright JL. Sarcomatoid urothelial carcinoma: Oncologic outcomes from a tertiary center and SEER-Medicare data. *J Clin Oncol* 38: 2020 (suppl; abstr e17033).

69. Diamantopoulos LN, Ngo S, Maldonado R, O'Malley RB, Laidlaw G, Fintelmann FJ, Holt SK, Gore JL, Schade GR, Lin DW, Grivas P, Montgomery RB, Hsieh AC, Cheng HH, Yezefski T, Schweizer MT, Yu EY, Wright JL, Psutka SP. Associations between baseline body composition and cancer-specific mortality following neoadjuvant chemotherapy and radical cystectomy for bladder cancer. *J Clin Oncol* 38: 2020 (suppl; abstr e17015).

70. Gravis G, Kolinsky MP, Mourey L, Piulats JM, Sridhar SS, Romano E, Berry WR, Gurney H, Retz M, Appleman LJ, Boegemann M, De Bono JS, Joshua AM, Emmenegger U, Conter HJ, Laguerre B, Wu H, Schloss C, Poehlein C, Yu EY. KEYNOTE-365 cohort B updated results: Pembrolizumab plus docetaxel and prednisone in abiraterone or enzalutamide-pretreated patients with metastatic castration-resistant prostate cancer. *European Association of Urology*; Abstract 560, 2020. 21st International European Association of Urology Virtual Meeting, July 2020.

71. Piulats JM, Yu EY, Gravis G, Laguerre B, Arranz J, Oudard S, Fong PCC, Kolinsky MP, Augustin M, Feyerabend S, Kam AE, Gurney H, Tafreshi A, Retz M, Berry WR, Mar N, Wu H, Schloss C, Poehlein C, De Bono JS. Pembrolizumab plus olaparib in docetaxel-pretreated patients with metastatic castration resistant prostate cancer: KEYNOTE-365 cohort A updated results. *European Association of Urology*; Abstract 561, 2020. 21st International European Association of Urology Virtual Meeting, July 2020.

72. Feyerabend S, Berry WR, Fong PCC, Piulats JM, Appleman LJ, Conter H, Shore N, Gravis G, Laguerre B, Gurney H, Retz M, Romano E, Mourey L, De Bono JS, Kam AE, Emmenegger U, Wu H, Schloss C, Poeehlein C, Yu EY. KEYNOTE 365 cohort C updated results: Pembrolizumab plus enzalutamide in abiraterone-pretreated patients with metastatic castration-resistant prostate cancer. *European Association of Urology*; Abstract 562, 2020. 21st International European Association of Urology Virtual Meeting, July 2020.

73. Marchioni M, Mir MC, Zargar H, Grivas P, Dall'era MAD, Spiess PES, Van Rhign BW, Lotan Y, Bivalacqua TJ, Holzerbeierlein JM, Thorpe A, Yu EY, Shariat SF, Kassouf W, Barocas DA, Daneshmand S, Dinney CP, McGrath JS, Sridhar SS, Wright J, North S, Stephenson AJ, Xylinas E, Black P. Nomogram predicting bladder cancer specific mortality after neoadjuvant chemotherapy and radical cystectomy for muscle-invasive bladder cancer: Results of an

international consortium. *European Association of Urology*; Abstract 1100, 2020. 21st International European Association of Urology Virtual Meeting, July 2020.

74. Soria F, Black PC, Fairey AS, Cookson MS, Yu EY, Kassouf W, Dall'era MA, Sridhar SS, Mcgrath JS, Wright JL, Thorpe AC, Morgan TM, Daneshmand S, Holzbeierlein JM, Bivalacqua TJ, North S, Barocas DA, Lotan Y, Grivas P, Stephenson AJ, Shah JB, Van Rhijn BW, Spiess PE, Shariat SF, Gontero P. *European Association of Urology*; Abstract PT406, 2020. 21st International European Association of Urology Virtual Meeting, July 2020.

75. O'Donnell P, Galsky MD, Rosenberg JE, Petrylak DP, Balar AV, McGregor BA, Heath E, Yu EY, Quinn DI, Hahn NM, Campbell M, Liang S-Y, Steinberg J, Loriot Y. EV-201: Long-term results of enfortumab vedotin monotherapy for locally advanced or metastatic urothelial cancer previously treated with platinum and PD-1/PD-L1 inhibitors. *Ann Oncol ESMO Congress*; Volume 31, Supplement 4, S579-S580. 2020 European Society of Medical Oncology Congress. Madrid, Spain, Sept. 2020. Virtual Poster presentation at ESMO Congress, Madrid, Spain, Sept. 2020.

76. Arranz Arija JA, Yu EY, Piulats JM, Gravis G, Laguerre B, Oudard S, Fong PC, Kolinsky MP, Augustin M, Todenhofer T, Kam AE, Gurney H, Tafreshi A, Retz M, Berry WR, Mar N, Wu H, Qiu P, Schloss C, de Bono JS. Pembrolizumab plus Olaparib in patients with docetaxel-pretreated metastatic castration-resistant prostate cancer: KEYNOTE-365 Cohort A update. *Ann Oncol ESMO Congress*; Volume 31, Supplement 4, S513-S514. 2020 European Society of Medical Oncology Congress. Madrid, Spain, Sept. 2020. Virtual Poster presentation at ESMO Congress, Madrid, Spain, Sept. 2020.

77. Romano E, Sridhar SS, Kolinsky MP, Gravis G, Mourey L, Piulats JM, Berry WR, Gurney H, Retz M, Appleman LJ, Boegemann M, de Bono JS, Joshua AM, Emmenegger U, Conter JH, Laguerre B, Wu H, Qiu P, Schloss C, Yu EY. Pembrolizumab plus docetaxel and prednisone in patients with abiraterone acetate- or enzalutamide-pretreated metastatic castration-resistant prostate cancer: KEYNOTE 365 Cohort B update. *Ann Oncol ESMO Congress*; Volume 31, Supplement 4, S512-S513. 2020 European Society of Medical Oncology Congress. Madrid, Spain, Sept. 2020. Virtual Poster presentation at ESMO Congress, Madrid, Spain, Sept. 2020.

78. Mourey L, Conter HJ, Shore N, Berry WR, Fong PC, Piulats JM, Appleman LJ, Todenhofer T, Gravis G, Laguerre B, Gurney H, Retz M, Romano E, de Bono JS, Kam AE, Emmenegger U, Wu H, Qiu P, Schloss C, Yu EY. Pembrolizumab plus enzalutamide in patients with abiraterone acetate-pretreated metastatic castration-resistant prostate cancer: KEYNOTE-365 Cohort C update. *Ann Oncol ESMO Congress*; Volume 31, Supplement 4, S516-S517. 2020 European Society of Medical Oncology Congress. Madrid, Spain, Sept. 2020. Virtual Poster presentation at ESMO Congress, Madrid, Spain, Sept. 2020.

79. Alva A, Csoszi T, Ozguroglu M, Matsubara N, Geczi L, Cheng SY-S, Fradet Y, Oudard S, Vulsteke C, Morales Barrera R, Flechon A, Gunduz S, Loriot Y, Rodriguez-Vida A, Mamtani R, Yu EY, Nam K, Imai K, Moreno BH, Powles TB. LBA23 - Pembrolizumab combined with chemotherapy vs. chemotherapy alone as first-line therapy for advanced urothelial carcinoma: KEYNOTE-361. *Ann Oncol ESMO Congress*; Volume 31, Supplement 4, S1155. 2020 European Society of Medical Oncology Congress. Madrid, Spain, Sept. 2020. Virtual Oral presentation at ESMO Congress, Madrid, Spain, Sept. 2020.

80. Yu EY, Park SH, Huang YH, Bennamoun M, Xu L, Kim J, Antonarakis EA. Phase 3 study of combination pembrolizumab + olaparib vs. enzalutamide/abiraterone in metastatic castration-resistant prostate cancer after progression on chemotherapy (KEYLYNK-010). *Journal for ImmunoTherapy of Cancer* Nov. Vol. 8, Suppl 3, P345. Virtual poster presentation at 2020 Society for Immunotherapy of Cancer at National Harbor, MD, Nov. 2020.

81. Joshua AM, Gurney H, Retz M, Tafreshi A, Fong PCC, Shore ND, Romano E, Augustin M, Piulats JM, Berry WR, Kolinsky MP, Sridhar SS, Conter HJ, Todenhofer T, Appleman LJ, Wu H, Schloss C, Poehlein CH, de Bono JS, Yu EY. Pembrolizumab combination therapies in patients with metastsatic castration-resistant prostate cancer: Cohorts A-C of the Phase 1b/2 KEYNOTE-365 study. *ESMO Asia Virtual Congress* 2020; Abstract 2170. Virtual Oral presentation at ESMO-Asia Congress, Singapore, Nov. 2020.

82. Hamilton E, Shapiro CL, Petrylak D, Boni V, Martin M, Del Conte G, Cortes J, Agrawal L, Arkenau HT, Tan AR, Debruyne P, Minchom A, Rutten A, Valdes-Albini F, Yu EY, Augustine B, D'Amelio A Jr, Barrios D, Hurvitz SA. Trastuzumab deruxtecan with nivolumab in patients with HER2-expressing, advanced breast cancer: a 2-part, phase 1b, multicenter, open-label study. *San Antonio Breast Cancer Symposium* 2020; PD3-07. Virtual Poster Spotlight presentation at 2020 San Antonio Breast Cancer Symposium, San Antonio, TX, Dec. 2020.

83. Balar AV, McGreggor B, Rosenberg J, van der Heijden MS,. Park SH, Lee JL, Harrison MR, Heath EI, Stein MN, Loriot Y, Necchi A, Steinberg J, Liang SY, Kim E, Trowbridge J, Campbell M, Petrylak DP, Yu EY. EV-201 Cohort 2: Enfortumab vedotin in cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer who received prior PD-1/PD-L1 inhibitors. *J Clin Oncol* 39, 2021 (suppl; abstr 394). **Oral presentation at Virtual Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2021.**

84. Wong RL, Ferris LA, Do OA, Holt SK, Ramos JD, Crabb S, Sternberg C, Bellmunt J, Ladoire S, De Giorgi U, Harshman L, Vaishampayan U, Necchi A, Srinivas S, Pal S, Niegisch G, Dorff TB, Galsky MD, Yu EY. Efficacy of platinum re-challenge in metastatic urothelial carcinoma: A retrospective comparison of various chemotherapy regimens. *J Clin Oncol* 39, 2021 (suppl; abstr 459). Poster presentation at Virtual Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2021.

85. Powles T, Csoszi T, Ozguroglu M, Matsubara N, Geczi L, Cheng SY, Fradet Y, Oudard S, Vulsteke C, Barrera RM, Flechon A, Gunduz S, Loriot Y, Rodriguez-Vida A, Mamtani R, Yu EY, Nam K, Imai K, Moreno BH, Alva A. First-line pembrolizumab vs. chemotherapy for choice-of-carboplatin patients with advanced urothelial carcinoma in KEYNOTE-361. *J Clin Oncol* 39, 2021 (suppl; abstr 450). Poster presentation at Virtual Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2021.

86. Wong RL, Cheng HH, Holt SK, Conrad N, Loesch H, Fernandez S, Sahoo R, Bauer Z, Toulouse AE, Grivas P, Yezefski T, Russell KJ, Wright JL, Schweizer MT, Montgomery RB, Lee JH, Chen DL, Zeng J, Lin DW, Yu EY. Use of fluciclovine PET/CT for prostate cancer: Initial results from a prospective registry at a tertiary academic center. *J Clin Oncol* 39, 2021 (suppl; abstr 29). Poster presentation at Virtual Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2021.

87. Loriot Y, Alva A, Csoszi T, Ozguroglu M, Matsubara N, Geczi L, Cheng SY, Fradet Y, Oudard S, Vulsteke C, Barrera RM, Flechon A, Gunduz S, Rodriguez-Vida A, Mamtani R, Yu EY, Liu CC, Imai

K, Moreno BH, Powles T. Post-hoc analysis of long-term outcomes in patients with CR, PR, or SD to pembrolizumab or platinum-based chemotherapy as first-line therapy for advanced urothelial carcinoma in KEYNOTE-361. *J Clin Oncol* 39, 2021 (suppl; abstr 435). Poster presentation at Virtual Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2021.

88. Alva A, Csoszi T, Ozguroglu M, Matsubara N, Geczi L, Cheng SY, Fradet Y, Oudard S, Vulsteke C, Barrera RM, Flechon A, Gunduz S, Loriot Y, Rodriguez-Vida A, Mamtani R, Yu EY, Nam K, Imai K, Moreno BH, Powles T. Impact of subsequent therapy on survival in KEYNOTE-361: Pembrolizumab plus chemotherapy or pembrolizumab alone versus chemotherapy as first-line therapy for advanced urothelial carcinoma. *J Clin Oncol* 39, 2021 (suppl; abstr 439). Poster presentation at Virtual Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2021.

89. Ozguroglu M, Alva A, Csoszi T, Matsubara N, Geczi L, Cheng SY, Fradet Y, Oudard S, Vulsteke C, Barrera RM, Flechon A, Gunduz S, Loriot Y, Rodriguez-Vida A, Mamtani R, Yu EY, Nam K, Imai K, Moreno BH, Powles T. Analysis of PFS2 by subsequent therapy in KEYNOTE-361: Pembrolizumab plus chemotherapy or pembrolizumab alone versus chemotherapy as first-line therapy for advanced urothelial carcinoma. *J Clin Oncol* 39, 2021 (suppl; abstr 448). Poster presentation at Virtual Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2021.

90. Sartor AO, Laidley D, Pouliot F, Probst S, Sabbagh R, Saad F, Stambler N, Yu EY. A multicenter, randomized, controlled phase II study: Efficacy and safety of PSMA-targeted radioligand therapy I-131-1095 plus enzalutamide in 18F-DCFPyL PSMA scan avid, metastatic castration-resistante prostate cancer patients post-abiraterone progression (ARROW). *J Clin Oncol* 39, 2021 (suppl; abstr TPS187). Poster presentation at Virtual Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2021.

91. Vapiwala N, Cho SY, Kyriakopoulos C, Chen YH, Duan F, McConathy J, Mankoff D, Wong TZ, McKay R, Beylergil V, Yu EY, Koontz B, Liu G, Carducci M. PET-directed local or systemic therapy intensification in prostate cancer patients with post-prostatectomy biochemical recurrence: A trial of the ECOG-ACRIN Cancer Research Group (EA8191). *J Clin Oncol* 39, 2021 (suppl; abstr TPS267). Poster presentation at Virtual Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2021.

92. Yu EY, Kang V, Walker L, Galsky MD. SGNTUC-019: Phase II basket study of tucatinib and trastuzumab in previously treated solid tumors with HER2 alterations: Urothelial cancer cohort. *J Clin Oncol* 39, 2021 (suppl; abstr TPS499). Poster presentation at Virtual Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2021.

93. Appleman L, Kolinsky MP, Berry WR, Retz M, Mourey L, Piulats JM, Romano E, Gravis G, Gurney H, de Bono JS, Boegemann M, Emmenegger U, Joshua A, Massard C, Sridhar SS, Conter HJ, Li XT, Schloss C, Poehlein CH, Yu EY. KEYNOTE-365 cohort B: Pembrolizumab plus docetaxel and prednisone in abiraterone or enzalutamide-pretreated patients with metastatic castration-resistant prostate cancer – New data after an additional 1 year of follow-up. *J Clin Oncol* 39, 2021 (suppl; abstr 10). **Oral presentation at Virtual Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2021.**

94. Schweizer MT, Sivakumar S, Tukachinsky H, Coleman I, De Sarkar N, Yu EY, Konnick EQ, Nelson P, Pritchard CC, Montgomery RB. Concordance of DNA damage repair gene mutations in paired primary and metastatic prostate cancer samples. *J Clin Oncol* 39, 2021 (suppl 15; abstr 5020). Poster presentation at 2021 ASCO Virtual Scientific Program, June 2021.

95. Stinchcombe T, Monk BJ, Okines AFC, Pohlmann PR, Yu EY, Bekaii-Saab TS, Nakamura Y, O'Malley DM, Kang V, Walker LN, Reck M. SGNTUC-019: Phase 2 basket study of tucatinib and trastuzumab in previously treated solid tumors with HER2 alterations. *J Clin Oncol* 39, 2021 (suppl 15; abstr TPS3151). Poster presentation at 2021 ASCO Virtual Scientific Program, June 2021.

96. De Bono JS, Cook N, Yu EY, Lara PN, Wang JS, Yamasaki Y, Yamamiya I, Gao P, Calleja EM, Rathkopf DE. First-in-human study of TAS3681, an oral androgen receptor antagonist with AR and AR splice variant downregulation activity, in patients with metastatic castration-resistant prostate cancer refractory to abiraterone and/or enzlutamide and chemotherapy. *J Clin Oncol* 39, 2021 (suppl 15; abstr 5031). Poster presentation at 2021 ASCO Virtual Scientific Program, June 2021.

97. Vapiwala N, Chen YH, Cho SY, Duan F, Kyriakopoulos C, Shevrin DH, McKay RR, Koontz BF, Yu EY, Beylergil V, Mankoff DA, McConathy J, Liu G, Wong TZ, Carducci MA. Phase III study of local or systemic therapy INtensification DIrected by PET in prostate CAncer patients with post-prostaTEctomy biochemical recurrence (INDICATE): ECOG-ACRIN EA8191. *J Clin Oncol* 39, 2021 (suppl 15; abstr TPS5098). Poster presentation at 2021 ASCO Virtual Scientific Program, June 2021.

98. Wong RL, Holt SK, Zeng J, Graham L, Kang R, Conrad N, Toulouse A, Bauer Z, Lai M, Yezefski T, Wright JL, Weg ES, Hsieh AC, Cheng HH, Lee JH, Chen DL, Lin DW, Yu EY. The fluciclovine (FACBC) PET/CT site-directed therapy of oligometastatic prostate cancer (Flu-BLAST-PC) trial. *J Clin Oncol* 39, 2021 (suppl 15; abstr TPS5099). Poster presentation at 2021 ASCO Virtual Scientific Program, June 2021.

99. McGregor BA, Balar AV, Rosenberg JE, Van Der Heijden MS, Park SH, Lee JL, Kojima T, Harrison MR, Heath EI, Stein MN, Loriot Y, Necchi A, Steinberg JL, Liang SY, Trowbridge J, Petrylak DP, Yu EY. Enfortumab vedotin in cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer who received prior PD-1/PD-L1 inhibitors: An updated analysis of EV-201 Cohort 2. *J Clin Oncol* 39, 2021 (suppl 15; abstr 4524). Poster presentation at 2021 ASCO Virtual Scientific Program, June 2021.

100. Nordquist LT, Yu EY, Piulats JM, Gravis G, Fong PCC, Todenhoefer T, Laguerre B, Arranz Arija JA, Oudard S, Massard C, Stoeckle M, Carles J, Kolinsky MP, Augustin M, Gurney H, Tafreshi A, Li XT, Poehlein CH, Schloss C, de Bono JS. Pembrolizumab plus Olaparib in patients with docetaxel-pretreated metastatic castration-resistant prostate cancer: Updated results from KEYNOTE-365 cohort A with a minimum of 11 months of follow-up for all patients. Abstract MP24-14, 2021. Poster (virtual) presentation at the 2021 Annual Meeting of the American Urological Association Education and Research, Inc., Las Vegas, NV, September 2021.

101. Schweizer M, Gulati R, Yezefski T, Cheng H, Sievers C, Dumpit R, Alexander K, McDonald N, Lai M, Nega K, Hammond J, Grivas P, Hsieh A, Montgomery B, Nelson P, Yu EY. Bipolar androgen therapy plus Olaparib in men with metastatic castration-resistant prostate cancer. *Annals of Oncology* (2021) 32 (suppl_5):S626-S677. Abstract 592P. ePoster presentation at ESMO Congress 2021.

102. Yu EY, Piulats JM, Gravis G, Fong P, Todenhofer T, Laguerre B, Arranz Arija J, Oudard S, Massard C, Stoeckle M, Nordquist LT, Carles J, Huang M, Li Y, Qiu P, Pohlein CH, Schloss C, de

Bono J. Association between homologous recombination repair mutations and response to pembrolizumab plus Olaparib in metastatic castration-resistant prostate cancer: KEYNOTE 365 Cohort A biomarker analysis. *Annals of Oncology* (2021) 32 (suppl_5):S382-S406. Abstract 73P. ePoster presentation at ESMO Congress 2021.

103. Yu EY, Piulats JM, Gravis G, Fong PCC, Todenhofer T, Laguerre B, Arranz Arija JA, Oudard S, Massard C, Stoeckle M, Nordquist LT, Carles J, Kolinsky MP, Augustin M, Gurney H, Tafreshi A, Li XT, Pohlein CH, Schloss C, de Bono J. Pembrolizumab plus Olaparib in patients with docetaxel-pretreated metastatic castration-resistant prostate cancer: Update of KEYNOTE-365 cohort A with a minimum of 11 months of follow-up for all patients. *Annals of Oncology* (2021) 32 (suppl_5):S626-S677. Abstract 612P. ePoster presentation at ESMO Congress 2021.

104. Shore ND, Kramer G, Joshua AM, Li XT, Pohlein CH, Schloss C, de Bono JS, Yu EY. KEYNOTE-365 cohort I: Phase Ib/II study of platinum containing chemotherapy in combination with pembrolizumab and chemotherapy alone for treatment-emergent neuroendocrine prostate carcinoma. *Annals of Oncology* (2021) 32 (suppl_5):S626-S677. Abstract 639TiP. ePoster presentation at ESMO Congress 2021.

105. De Bono JS, Shore ND, Kramer G, Joshua AM, Li XT, Poehlein CH, Schloss C, Yu EY. Phase Ib/II trial of pembrolizumab + vibostolimab combination therapy in patients with adenocarcinoma metastatic castration-resistant prostate cancer or treatment-emergency neuroendocrine metastatic castration-resistant prostate cancer: KEYNOTE-365 cohorts G and H. *Annals of Oncology* (2021) 32 (suppl_5):S626-S677. Abstract 641TiP. ePoster presentation at ESMO Congress 2021.

106. Kramer G, Shore ND, Joshua AM, Li XT, Poehlein CH, Schloss C, de Bono JS, Yu EY. Phase 1b/II trial of pembrolizumab + Lenvatinib combination therapy in patients with adenocarcinoma metastatic castration-resistant prostate cancer or treatment-emergenct neuroendocrine metastatic castration-resistant prostate cancer. KEYNOTE-365 cohorts E and F. *Annals of Oncology* (2021) 32 (suppl_5):S626-S677. Abstract 640TiP. ePoster presentation at ESMO Congress 2021.

107. Reck M, Okines A, Pohlmann PR, Yu EY, Bekaii-Saab T, Nakamura Y, Monk BJ, O'Malley D, Kang V, Walker LN, Stinchcombe T. SGNTUC-019: Phase II basket study of tucatinib and trastuzumab in previously treated solid tumors with HER2 alterations. *Annals of Oncology* (2021) 32 (suppl_5):S583-S620. Abstract 557TiP. ePoster presentation at ESMO Congress 2021.

108. De Bono J, Shore N, Kramer G, Joshua A, Li XT, Poehlein C, Schloss C, Yu EY. Phase 1b/2 KEYNOTE-365 cohort I: Platinum-containing chemotherapy alone or in combination with pembrolizumab for treatment-emergent neuroendocrine prostate carcinoma. *J Immunother Cancer* 2021:9:418a. Poster presentation at 2021 Society for Immunotherapy of Cancer at Washington, DC, Nov. 2021.

109. Kramer G, Shore N, Joshua A, Li XT, Poehlein C, Schloss C, De Bono J, Yu EY. Pembrolizumab + Lenvatinib in patients with adenocarcinoma metastatic castration-resistant prostate cancer or treatment-emergent neuroendocrine metastatic castration-resistant prostate cancer: Phase 1b/2 KEYNOTE-365 cohorts E/F. *J Immunother Cancer* 2021:9:419a. Poster presentation at 2021 Society for Immunotherapy of Cancer at Washington, DC, Nov. 2021.

110. Shore N, De Bono J, Kramer G, Joshua A, Li XT, Poehlein C, Schloss C, Yu EY. Pembrolizumab + vibostolimab in patients with adenocarcinoma metastatic castration-resistant prostate cancer or treatment-emergent neuroendocrine metastatic castration-resistant prostate cancer: Phase 1b/2 KEYNOTE-365 cohorts G/H. *J Immunother Cancer* 2021:9:425a. Poster presentation at 2021 Society for Immunotherapy of Cancer at Washington, DC, Nov. 2021.

111. Appelman L, Todenhoefer T, Berry W, Gurney H, Retz M, Conter H, Laguerre B, Fong P, Ferrario C, Gravis G, Piulats J, Emmenegger U, Shore N, Romano E, Mourey L, Li XT, Poehlein C, Schloss C, De Bono J, Yu EY. KEYNOTE-365 cohort C: Pembrolizumab + enzalutamide in patients with abiraterone acetate pretreated metastatic castration-resistant prostate cancer – data after minimum of 22 months of follow-up. *J Immunother Cancer* 2021:9:347a. Poster presentation at 2021 Society for Immunotherapy of Cancer at Washington, DC, Nov. 2021.

112. Piulats J, Ferrario C, Linch M, Stoeckle M, Laguerre B, Arranz J, Todenhoefer T, Fong P, Berry W, Emmenegger U, Mourey L, Mar N, Appelman L, Joshua A, Conter H, Li XT, Schloss C, Poehlein C, De Bono J, Yu EY. KEYNOTE-365 cohort D: Pembrolizumab + abiraterone acetate and prednisone in patients with chemotherapy-naive metastatic castration-resistant prostate cancer. *J Immunother Cancer* 2021:9:351a. Poster presentation at 2021 Society for Immunotherapy of Cancer at Washington, DC, Nov. 2021.

113. Ho M, Ma J, Black A, Zargar H, Sridhar S, D'Andrea D, Soria F, Fairey A, Mertens L, Dinney C, Mir MC, Krabbe LM, Cookson M, Jacobsen N, Montgomery J, Vasdev N, Yu EY, Xylinas E, Campain N, Kassouf Wm, Dall'era M. The effect of cisplatin-based neoadjuvant chemotherapy on the renal function of patients undergoing radical cystectomy. *Society of Urologic Oncology* Poster #177. Poster presentation at 22nd Annual Meeting of the Society of Urologic Oncology at Orlando, FL, Dec. 2021.

114. Psutka SP, Gore J, Schade G, Grivas P, Hsieh A, Lee J, Montgomery B, Schweizer M, Yezefski T, Yu EY, Chen J, Liao J, Weg E, Zeng J, Holt S, Dwyer E, Alving T, Jannat S, Wright J. Prospective evaluation of a comprehensive geriatric assessment in multidisciplinary bladder cancer care: Feasibility and impact on decisional conflict. *Society of Urologic Oncology* Poster #227. Poster presentation at 22nd Annual Meeting of the Society of Urologic Oncology at Orlando, FL, Dec. 2021.

115. Galsky MD, Ramos J, Tan Q, Yu EY. SGNTUC-019: Phase 2 basket study of tucatinib and trastuzumab in previously treated solid tumors with HER2 alterations – urothelial cancer cohort. *J Clin Oncol* 40, 2022 (suppl 6; abstr TPS586). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2022.

116. Maldonado R, Fintelmann FJ, Marquardt JP, O'Malley RB, Holt SK, Ngo S, Diamantopoulos LK, Laidlaw G, Schade GR, Lin DW, Wright JL, Gore JL, Nyame YA, Grivas P, Yu EY, Montgomery RB, Hsieh AC, Yezefski R, Schweizer MT, Psutka SP. Changes in body composition during neoadjuvant platinum-based chemotherapy associations prior to radical cystectomy: Implications for chemotherapy-associated adverse events and oncologic outcomes. *J Clin Oncol* 40, 2022 (suppl 6; abstr 476). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2022.

117. Kramer G, Shore ND, Joshua AM, Li XT, Poehlein CH, Schloss C, De Bono JS, Yu EY. KEYNOTE-365 cohorts E and F: Phase 1b/2 study of pembrolizumab + lenvatinib combination therapy in patients with adenocarcinoma metastatic castration-resistant prostate cancer or treatment-

emergent neuroendocrine metastatic castration-resistant prostate cancer. *J Clin Oncol* 40, 2022 (suppl 6; abstr TPS215). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2022.

118. Shore ND, De Bono JS, Kramer G, Joshua AM, Li XT, Poehlein CH, Schloss C, Yu EY. KEYNOTE-365 cohorts G and H: Phase 1b/2 study of pembrolizumab + vibostolimab combination therapy in patients with adenocarcinoma metastatic castration-resistant prostate cancer or treatment-emergent neuroendocrine metastatic castration-resistant prostate cancer. *J Clin Oncol* 40, 2022 (suppl 6; abstr TPS204). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2022.

119. De Bono JS, Joshua AM, Shore ND, Kramer G, Li XT, Poehlein CH, Schloss C, Yu EY. KEYNOTE-365 cohort I: Phase 1b/2 study of pembrolizumab combined with platinum-containing chemotherapy and chemotherapy alone for treatment-emergent neuroendocrine prostate carcinoma. *J Clin Oncol* 40, 2022 (suppl 6; abstr TPS218). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2022.

120. Psutka SP, Gore J, Holt SK, Dwyer E, Schade G, Grivas P, Hsieh AC, Lee JK, Montgomery RB, Schweizer MT, Yezefski T, Yu EY, Chen JJ, Liao JJ, Weg ES, Zeng J, Alving T, Jannat S, Wright J. Prospective evaluation of a comprehensive geriatric assessment in multidisciplinary bladder cancer care: Feasibility and impact on decisional conflict. *J Clin Oncol* 40, 2022 (suppl 6; abstr 479). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2022.

121. Sokolova A, Gulati R, Cheng HH, Beer TM, Graff JN, Amador M, Toulouse A, Taylor K, Bailey S, Smith S, Tabatabaei S, Sinit R, Slottke R, Vuky J, Yezefski T, Grivas P, Yu EY, Schweizer MT. Durvalumab and Olaparib for the treatment of prostate cancer in men predicted to have a high neoantigen load. *J Clin Oncol* 40, 2022 (suppl 6; abstr TPS202). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2022.

122. Sonpavde GP, Maughan BL, McGregor BA, Wei XX, Kilbridge KL, Lee RJ, Yu EY, Schweizer MT, Montgomery RB, Cheng HH, Hsieh AC, Jain RK, Grewal JS, Pico C, Gafoor Z, Perschy TP, Grivas P. Phase 2 trial of CV301 vaccine plus atezolizumab in advanced urothelial carcinoma. *J Clin Oncol* 40, 2022 (suppl 6; abstr 511). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2022.

123. Ferrario C, Piulats JM, Linch MD, Stoeckle M, Laguerre B, Arranz JA, Todenhofer T, Fong PCC, Berry WR, Emmenegger U, Mourey L, Mar N, Appleman LJ, Joshua AM, Conter HJ, Li XT, Schloss C, Poehlein CH, De Bono JS, Yu EY. Pembrolizumab plus abiraterone acetate and prednisone in patients with chemotherapy-naïve metastatic castration-resistant prostate cancer: Results from KEYNOTE-365 cohort D. *J Clin Oncol* 40, 2022 (suppl 6; abstr 118). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2022.

124. Csoszi T, Powles T, Alva AS, Castellano DE, Ozguroglu M, O'Donnell PH, Loriot Y, Hahn NM, Flechon A, Rodriguez-Vida A, De Wit R, Cheng SY, Oudard S, Vulsteke C, Yu EY, Lin J, Imai K, Moreno BH, Balar AV, Grivas P. First-line pembrolizumab in advanced urothelial carcinoma: Clinical parameters associated with efficacy in the phase 2 KEYNOTE-052 and phase 3 KEYNOTE-361 trials. *J Clin Oncol* 40, 2022 (suppl 6; abstr 521). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2022.

125. Galsky MD, Del Conte G, Foti S, Yu EY, Machiels JPH, Doger B, Necchi A, De Braud FG, Hamilton EP, Hennequin A, Van den Mooter T, Debruyne PR, Moreno I, Arkenau HT, Tsuchihashi Z, Cheng FC, Augustine B, Cheng B, Barrios D, Luftner D. Primary analysis from DS8201-A-U105: A phase 1b, 2-part, open-label study of trastuzumab deruxtecan with nivolumab in patients with HER2-expressing urothelial carcinoma. *J Clin Oncol* 40, 2022 (suppl 6; abstr 438). Rapid Abstract Session Oral presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2022.

126. Urtishak K, Attard G, Kanno T, Thomas S, Mason GE, Espina B, Hutnick N, Guckert M, del Corral A, Li M, Lopez-Gitlitz A, Chi K, Kelly WK, Yu EY, Fizazi K, Smith M. High prevalence and heterogeneity of emergence of BRCA reversion mutations at progression on niraparib treatment in *BRCA*-mutant metastatic castration-resistant prostate cancer patients. Abstract 4133/17. Poster presentation at American Association for Cancer Research, New Orleans, LA, Apr. 2022.

127. Ghali F, Roudier M, Vakar-Lopez F, Garcia J, Wang Y, Ha G, Grivas P, Lee J, Yu EY, Montgomery B, Hsieh AC, Wright JL, Lam HM. Antibody drug conjugates and variant histology muscle-invasive bladder cancer: Are the targets present in primary and/or metastatic tumors? Abstract PD53-09. *J Urol* Vol. 207, No. 5S:e913. Poster presentation at American Urological Association 2022 Annual Meeting, New Orleans, LA, May 2022.

128. Phuong A, Marquardt JP, Fintelmann FJ, O'Malley R, Laidlaw G, Eagle Z, Ngo S, Holt S, Orcutt D, Schade GR, Lin DW, Schweizer MT, Yezefski T, Yu EY, Montgomery B, Grivas P, Psutka S. Declines in skeletal muscle mass and quality during cytotoxic chemotherapy predict increased risk of chemotherapy-associated adverse events in men with testis cancer. Abstract MP46-12. *J Urol* Vol. 207, No. 5S:e777. Poster presentation at American Urological Association 2022 Annual Meeting, New Orleans, LA, May 2022.

129. Makrakis D, Roudier M, Wang Y, Vakar-Lopez F, Garcia J, Dash A, Lin DW, Schade G, Mostaghel EA, Cheng HH, Schweizer MT, Holt SK, Gore JL, Yu EY, Lam HM, Wright JL, Montgomery B. A phase 1/2 study of rapamycin and cisplatin/gemcitabine for treatment of patients with muscle-invasive bladder cancer. Abstract PD10-06. *J Urol* Vol. 207, No. 5S:e185. Poster presentation at American Urological Association 2022 Annual Meeting, New Orleans, LA, May 2022.

130. Noonavath M, Mun K, Marquardt P, Fintelmann FJ, O'Malley R, Holt SK, Dwyer E, Maldonado R, Diamantopoulos L, Makrakis D, Laidlaw G, Schade GR, Lin DW, Wright JL, Gore JL. Associations between skeletal muscle gauge and survival following radical cystectomy for bladder cancer: A novel assessment of muscle mass and quality. Abstract MP56-06. *J Urol* Vol. 207, No. 5S:e973. Poster presentation at American Urological Association 2022 Annual Meeting, New Orleans, LA, May 2022.

131. Garcia J, Vakar-Lopez F, Roudier M, Grivas P, Yu EY, Cheng HH, Schweizer MT, Haffner M, Lee JK, Corey E, Montgomery B, Hsieh AC, Wright JL, Lam HM. Urothelial cancer rapid autopsy program: Biospecimens and patient-derived preclinical models. Abstract MP06-05. *J Urol* Vol. 207, No. 5S:e78. Poster presentation at American Urological Association 2022 Annual Meeting, New Orleans, LA, May 2022.

132. Yu EY, Pieczonka CM, Armstrong AJ, Suzuki H, Bailen JL, Murphy DG, Lebret T, Luz M, Thiery-Vuillemin A, Ortiz JA, Khan J, Briganti A. DARolutamide ObservationaL (DAROL) study in

patients with nonmetastatic castration-resistant prostate cancer. *J Clin Oncol* 40, 2022 (suppl 16; abstr e17029).

133. Gulhane A, Talukder R, Dash A, Ellis WJ, Schade G, Chen JJ, Weg ES, Cheng HH, Grivas P, Hawley J, Lee JK, Montgomery RB, Nelson PS, Schweizer MT, Yezefski TY, Yu EY, Lin DW, Cheng DL. Clinical impact of PSMA PET in patients with biochemically recurrent prostate cancer after locoregional definitive therapy. *J Clin Oncol* 40, 2022 (suppl 16; abstr e17009).

134. Sokolova A, Gulati R, Cheng HH, Beer TM, Graff JN, Amador M, Toulouse A, Taylor K, Bailey S, Smith S, Tabatabaei S, Sinit R, Slottke R, Vuky J, Yezefski T, Grivas P, Yu EY, Schweizer MT. Durvalumab and Olaparib for the treatment of prostate cancer in men predicted to have a high neoantigen load. *J Clin Oncol* 40, 2022 (suppl 16; abstr TPS5099). Poster presentation at ASCO Annual Meeting, Chicago, IL, Jun. 2022.

135. Wong RL, Cheng HH, Fann JR, Hnida J, Chakoian M, Schenker Y, Yu EY, Gore JL. Longitudinal screening for depression and anxiety in prostate cancer and association with disease and treatment factors. *J Clin Oncol* 40, 2022 (suppl 16; abstr 5023). Poster presentation at ASCO Annual Meeting, Chicago, IL, Jun. 2022.

136. Gulhane A, Talukder R, Wu ZJ, Lin DW, Dash A, Ellis WJ, Nyame YA, Schade G, Wright JL, Apisarnthanarax S, Chen J, Liao JL, Wallner K, Weg ES, Cheng HH, Grivas P, Hawley J, Hsieh AC, Lee JK, Montgomery B, Nelson PS, Schweizer MT, Yezefski T, Yu EY, Cheng DL. [^{68}Ga]-PSMA-11 can clarify equivocal lesions on conventional imaging and change management decisions among men with previously treated prostate cancer. Poster presentation at Society of Nuclear Medicine and Molecular Imaging Annual Meeting, Vancouver, BC, Jun. 2022.

137. Yu EY, Park SH, Goh JC, Shin SJ, Mehra N, McDermott R, Sala Gonzalez N, Fong P, Greil R, Retz M, Sade JP, Huang YH, Begbie SD, Rey F, Kramer G, Suzuki H, Zhang J, Kim J, Poehlein C, Antonarakis ES. Pembrolizumab plus Olaparib vs. abiraterone or enzalutamide for patients with previously treated metastatic castration-resistant prostate cancer: Randomized open-label phase 3 KEYLYNK-010 study. **Oral presentation at ESMO Congress 2022**, Paris, France, Sept 2022**.**

138. Kramer G, de Bono J, Joshua AM, Shore ND, Zhu P, Poehlein CH, Schloss C, Yu EY. Phase 1b/2 study of pembrolizumab plus Lenvatinib, vibostolimab, or platinum-based chemotherapy for adenocarcinoma metastatic castration-resistant prostate cancer or neuroendocrine metastatic prostate cancer: KEYNOTE-365 cohorts E-I. Poster presentation at ESMO Congress 2022, Paris, France, Sept 2022**.**

139. Linch MD, Ferrario C, Stoeckle M, Laguerre B, Arranz J, Todenhofer T, Fong P, Piulats JM, Berry W, Emmenegger U, Mourey L, Mar N, Appleman L, Joshua AM, Conter H, Li XT, Schloss C, Poehlein C, de Bono JS, Yu EY. Two year follow-up of KEYNOTE-365 Cohort D: Pembrolizumab plus abiraterone acetate and prednisone in patients with chemotherapy-naïve metastatic castration-resistant prostate cancer. Poster presentation at ESMO Congress 2022, Paris, France, Sept 2022**.**

140. Galsky MD, O'Donnell PH, Burgess E, Van der Heijden M, Krieger L, Necchi A, Yu EY, Matsubara N, Campbell MT, Gadde S, Aragon-Ching JB, Koshkin VS, Zhang W, Sokolowski K, Powles T. Phase 2 clinical study evaluating the efficacy and safety of distamab vedotin with or without

pembrolizumab in patients with HER2-expressing urothelial carcinoma (RC48G001, TIP). Poster presentation at 2022 Society for Immunotherapy of Cancer at Boston, MA, Nov. 2022.

INVITED TALKS AND LECTURES

UNIVERSITY/LOCAL CONFERENCES

- Program in Prostate Cancer Research/SPORE: "Retroviral RNA interference: systems development, biologic discoveries with telomerase, and future applications." Fred Hutchinson Cancer Research Center, Seattle, WA. March 4, 2004.
- Jobson Education: "Hormone refractory prostate cancer: Early vs. late vs. asymptomatic" Seattle, WA. June 24, 2005.
- Hematology/Oncology Fellows' Lecture Series: "Bladder cancer: Clinical implications." Fred Hutchinson Cancer Research Center, Seattle, WA. October 21, 2005.
- Resident Teaching Conference: "A case-based approach to managing metastatic bone disease." University of Washington, Seattle, WA. October 25, 2005.
- Seattle Cancer Care Alliance Physician Educational Outreach Program: "Hormone-refractory prostate cancer; the medical oncologist's perspective." Mount Vernon, WA. October 25, 2005.
- Breast and Prostate Program Bone Metastases Retreat: "Response to treatment in patients with metastatic prostate cancer: using PET scans as a surrogate marker for bone-dominant disease." Fred Hutchinson Cancer Research Center, Seattle, WA. November 14, 2005.
- Puget Sound Oncology Consortium's Annual Highlights of ASCO meeting: "Genitourinary Oncology ASCO 2006: review of prostate, bladder and testicular cancer." Seattle, WA. June 29, 2006.
- 6th Annual Pacific Northwest Prostate Cancer Conference: "A rising PSA after local therapy…implications and utility of PSA kinetics." Seattle, WA. September 16, 2006.
- Nuclear Medicine Internal Advisory Board: "Metabolic Imaging in prostate cancer – the future with PET." University of Washington, Seattle, WA. September 25, 2006.
- Program in Prostate Cancer Research/SPORE: "PET measures response to therapy in prostate cancer." University of Washington, Seattle, WA. November 2, 2006.
- North Star Lodge: "New concepts in genitourinary oncology." Yakima, WA. November 9, 2006.
- Nuclear Medicine External Advisory Board: "Metabolic imaging of prostate cancer as a biomarker of treatment response." University of Washington, Seattle, WA. November 30, 2006.
- Asian Senior Concerns Foundation: "Bladder cancer – the basics." Bellevue, WA. January 20, 2007.
- Asian Senior Concerns Foundation: "Prostate cancer PSA screening, treatments, and public concerns." Bellevue, WA. January 20, 2007.
- Virginia Mason Medical Center: "Mediastinal germ cell tumors." Seattle, WA. February 1, 2007.
- Hematology/Oncology Fellows' Lecture Series: "Bladder cancer: the need for new knowledge." Fred Hutchinson Cancer Research Center, Seattle, WA. March 2, 2007.
- A&P Lecture: "Imaging biomarkers in prostate cancer: the potential impact of tumor metabolism on clinical trials and drug development." University of Washington, Seattle, WA. March 6, 2007.
- Pacific Northwest SPORE: "Positron emission tomography imaging of bone in patients with metastatic prostate cancer." Fred Hutchinson/University of Washington Cancer Center Support Grant, Seattle, WA. May 21, 2007.
- Patient Power Radio Show: "Prostate, bladder, and testicular cancer update: ASCO 2007." Seattle, WA. June 10, 2007.

- Puget Sound Oncology Consortium Annual Highlights of ASCO meeting: "ASCO 2007 prostate cancer review." Seattle, WA. June 28, 2007.
- Emerging Trends in Oncology: "Update in prostate cancer, ASCO review." Seattle, WA. June 30, 2007.
- Patient Power Radio Show: "Prostate cancer: who to treat and when." Seattle, WA. July 11, 2007.
- American College of Physicians, Seattle Internal Medicine Board Review Course: "Solid tumor oncology cases." Seattle, WA. July 13, 2007.
- University of Washington Internal Medicine Residents' Educational Lecture Series: "Prostate cancer – A chronic disease." University of Washington, Seattle, WA. October 31, 2007.
- Oncology Grand Rounds: "A case of urothelial carcinoma of the bladder with leukemoid reaction: was GCSF playing a negative role?" Fred Hutchinson Research Center, Seattle, WA. November 6, 2007.
- Hematology/Oncology Fellows' Lecture Series: "Germ cell tumors/testicular cancer – what you really need to know." Fred Hutchinson Cancer Research Center, Seattle, WA. November 16, 2007.
- Program in Prostate Cancer Research/SPORE: "Positron emission tomography imaging of bone in patients with metastatic prostate cancer." Fred Hutchinson Cancer Research Center, Seattle, WA. March 6, 2008.
- Gilda's Club: "Advanced prostate cancer: an update on hormones, chemotherapy, and clinical trials." Seattle, WA. March 29, 2008.
- Hematology/Oncology Fellows' Lecture Series: "Bladder cancer: An unmet need." Fred Hutchinson Cancer Research Center, Seattle, WA. May 2, 2008.
- Patient Power Radio Show: "Prostate cancer biomarkers." Seattle, WA. May 7, 2008.
- 8th Annual Pacific Northwest Prostate Cancer Conference: "When is PSA useful? Why it may not always be reliable?" Fred Hutchinson Cancer Research Center. September 27, 2008.
- Seattle Cancer Care Alliance Network Physician Educational Outreach Program - Multicare Tacoma: "Bladder cancer – an unmet need." Tacoma, WA. September 30, 2008.
- Program in Prostate Cancer Research/SPORE: "Bone health for men with prostate cancer." Fred Hutchinson Cancer Research Center, Seattle, WA. November 6, 2008.
- Hematology/Oncology Educational Lecture Series: "Germ cell tumors/testicular cancer - a boards exam favorite." Fred Hutchinson Cancer Research Center, Seattle, WA. April 3, 2009.
- University of Washington CME Current Concepts in Drug Therapy: "Primary care issues for patients with prostate cancer undergoing androgen deprivation therapy." Seattle, WA. May 8, 2009.
- Seattle Cancer Care Alliance Scientific Lunch: "Drug development for prostate cancer – rebounding well from tough times." Seattle Cancer Care Alliance, Seattle, WA. June 11, 2009.
- Radiation Oncology Residents' Educational Lecture Series: "PSA kinetics to drive decision making for men with prostate cancer." University of Washington, Seattle, WA. June 18, 2009.
- Pacific Northwest SPORE Retreat: "PET imaging as a prostate cancer bone biomarker." University of British Columbia, Vancouver, BC. July 10, 2009.
- American College of Physicians, Seattle Internal Medicine Board Review Course: "Solid tumor oncology cases." Seattle, WA. July 17, 2009.
- Scripps 6th Annual Oncology Update: "ASCO review of prostate cancer." Seattle, WA. July 25, 2009.
- Hematology/Oncology Fellows' Lecture Series: "Bladder cancer: is it our turn yet?" Fred Hutchinson Cancer Research Center, Seattle, WA. August 21, 2009.
- Virginia Mason Community Journal Review: "Androgen deprivation therapy induced estrogen deficiency side effects." Seattle, WA. October 13, 2009.

- Seattle Cancer Care Alliance Network Physician Educational Outreach Program – Skagit Valley and Olympic Medical Centers: "Upcoming new drugs for prostate cancer therapy." Mt. Vernon, WA. October 15, 2009.
- Center for Biomedical Continuing Education: "Bone health across the cancer continuum: Updates and insight to an evolving story." Seattle, WA. January 28, 2010.
- Oncology Grand Rounds: "Prostate cancer and broken bones? Only from sticks and stones…" Fred Hutchinson Cancer Research Center, Seattle, WA. March 9, 2010.
- Hematology/Oncology Fellow's Lecture Series: "Germ cell tumors/testicular cancer – hitting the ball out of the park." Fred Hutchinson Cancer Research Center, Seattle, WA. March 26, 2010.
- 13th Annual Advanced Prostate Brachytherapy Conference: "Managing androgen deprivation therapy associated side effects." Seattle Prostate Institute, Seattle, WA. May 14, 2010.
- American College of Physicians, Seattle Internal Medicine Board Review Course: "Solid tumor oncology cases." Seattle, WA. July 23, 2010.
- Scripps 7th Annual Oncology Update: "Prostate cancer update: New therapies for castration-resistant disease." Seattle, WA. August 14, 2010.
- Patient Power Radio Show: "New treatments for prostate cancer." Seattle, WA. August 27, 2010.
- University of Washington Comprehensive Oncology Review: "Bladder cancer – keeping in the loop." Seattle, WA. October 2, 2010.
- University of Washington Comprehensive Oncology Review: "Germ cell tumors/testicular cancer – keeping an eye on the ball." Seattle, WA. October 3, 2010.
- Sanofi-Aventis Roundtable Program: "Cabazitaxel: A new option for metastatic hormone-refractory prostate cancer following a docetaxel containing regimen." Seattle, WA. October 7, 2010.
- 10th Annual Pacific Northwest Prostate Cancer Conference: "Protecting bone for prostate cancer patients." Fred Hutchinson Cancer Research Center, Seattle, WA. October 9, 2010.
- Multicare Tacoma: "Cabazitaxel: A new option for metastatic hormone-refractory prostate cancer following a docetaxel containing regimen." Tacoma, WA. November 16, 2010.
- Hematology/Oncology Fellows' Lecture Series: "Bladder cancer: getting in the loop." Fred Hutchinson Cancer Research Center, Seattle, WA. November 19, 2010.
- Science over Lunch: "Rapidly changing paradigms in prostate cancer – new FDA approvals and local contributions." Fred Hutchinson Cancer Research Center, Seattle, WA. March 10, 2011.
- Hematology/Oncology Educational Lecture Series: "Germ cell tumors/testicular cancer." Fred Hutchinson Cancer Research Center, Seattle, WA. March 11, 2011.
- Pacific Northwest Prostate Cancer SPORE: "Metabolic imaging and biomarkers to monitor treatment response of castration-resistant prostate cancer." Fred Hutchinson Cancer Research Center, Seattle, WA. March 28, 2011.
- Nuclear Medicine U01 Meeting: "Discerning Cabozantinib (XL184) biology with ^{11}C-acetate and ^{18}F-fluoride PET/CT imaging." Seattle Cancer Care Alliance, Seattle, WA. April 12, 2011.
- Scripps 8th Annual Oncology Update: "Genitourinary cancer update." Seattle, WA. August 13, 2011.
- University of Washington Comprehensive Oncology Review (2nd Annual): "Germ cell tumors/testicular cancer." Seattle, WA. September 18, 2011.
- University of Washington Comprehensive Oncology Review (2nd Annual): "Genitourinary Cancer Cases - Question and Answer Session." Seattle, WA. September 18, 2011.
- Hematology/Oncology Fellows' Lecture Series: "Bladder cancer: updates and local research endeavors." Fred Hutchinson Cancer Research Center, Seattle, WA. October 28, 2011.
- Hematology/Oncology Fellows' Solid Tumor Conference: "Prostate cancer: local research efforts." Seattle Cancer Care Alliance, Seattle, WA. October 28, 2011.

- Program in Prostate Cancer Research/SPORE: "Hormone-sensitive prostate cancer – updates on recent and ongoing clinical trials." Fred Hutchinson Cancer Research Center, Seattle, WA. November 3, 2011.
- Uganda Cancer Institute: "Cases from Kampala – prostate cancer case conference." Fred Hutchinson Cancer Research Center, Seattle, WA. June 14, 2012.
- University of Washington Comprehensive Oncology Review (3rd Annual): "Germ cell tumors/testicular cancer." Seattle, WA. September 23, 2012.
- Hematology/Oncology Fellows' Lecture Series: "Germ cell tumors/testicular cancer." Fred Hutchinson Cancer Research Center, Seattle, WA. October 12, 2012.
- Updates in Oncology and Blood/Marrow Transplantation – A Spotlight on Seattle Cancer Care Alliance: "Research advancements for castration-resistant prostate cancer." Seattle, WA. October 15, 2012.
- Hematology/Oncology Fellows' Lecture Series: "Bladder cancer: the next big thing in genitourinary oncology." Fred Hutchinson Cancer Research Center, Seattle, WA. November 2, 2012.
- Program in Prostate Cancer Research/SPORE: "Prostate cancer bone biomarkers: clinical trial tool or ready for prime time in the clinic?" Fred Hutchinson Cancer Research Center, Seattle, WA. March 7, 2013.
- Institute for Prostate Cancer Research 2013 Symposium – Breakthroughs in prostate cancer research: "Imaging advanced prostate cancer – beyond finding the tumor." Fred Hutchinson Cancer Research Center, Seattle, WA. March 17, 2013.
- Uganda Cancer Institute: "Cases from Kampala – prostate cancer case conference." Fred Hutchinson Cancer Research Center, Seattle, WA. July 11, 2013.
- Pacific Northwest Cancer SPORE Retreat 2013: "Identification of molecular characteristics of prostate cancer with ^{11}C-acetate and ^{18}F-FDG PET/CT-directed rapid autopsy." Fred Hutchinson Cancer Research Center, Seattle, WA. July 12, 2013.
- Seattle Cancer Care Alliance Network Physician Educational Outreach Program - Multicare Tacoma: "Recent and future therapeutic advancements for metastatic castration-resistant prostate cancer." Tacoma, WA. July 19, 2013.
- Medical Oncology Faculty Sections Meeting: "Fellowship Updates 2013." Seattle Cancer Care Alliance, Seattle, WA. August 1, 2013.
- Hematology/Oncology Educational Lecture Series: "Germ cell tumors/testicular cancer." Fred Hutchinson Cancer Research Center, Seattle, WA. September 13, 2013.
- University of Washington Comprehensive Oncology Review (4th Annual): "Germ cell tumors/testicular cancer." Seattle, WA. October 1, 2013.
- The Everett Clinic: "Cancer immunotherapy – fundamental concepts and emerging role." Everett, WA. October 1, 2013.
- Pacific Northwest SPORE Advocacy Meeting: "Sequencing of novel secondary hormonal therapies in metastatic castration-resistant prostate cancer." Fred Hutchinson Cancer Research Center, Seattle, WA. December 12, 2013.
- Program in Prostate Cancer Research/SPORE: "A review of PET imaging for prostate cancer: past, present and future." Fred Hutchinson Cancer Research Center, Seattle, WA. March 27, 2014.
- Institute for Prostate Cancer Research 2014 Symposium – Breakthroughs in prostate cancer research: "Imaging prostate cancer – present and future." Fred Hutchinson Cancer Research Center, Seattle, WA. April 12, 2014.
- Multicare Tacoma: "Overcoming cancer immunoevasion: the role of immunotherapy." Tacoma, WA. April 17, 2014.

- Seattle Cancer Care Alliance Network Physician Educational Outreach Program: "Role of immunotherapy for bladder cancer – a focus on the PDL1/PD1 axis." Bellevue, WA. June 25, 2014.
- Pacific NorthWest Prostate Cancer SPORE Retreat: "Clinical Core D." Fred Hutchinson Cancer Research Center, Seattle, WA. July 21, 2014.
- Hematology/Oncology Fellows' Lecture Series: "Germ cell tumors/testicular cancer." Fred Hutchinson Cancer Research Center, Seattle, WA. September 5, 2014.
- Seattle Cancer Care Alliance Network Physician Educational Outreach Program – Skagit Valley Medical Center: "The promise of immunotherapy for bladder cancer." Mt. Vernon, WA. September 17, 2014.
- Seattle Cancer Care Alliance Network Physician Educational Outreach Program – Bend Memorial Clinic: "The promise of immunotherapy for bladder cancer." Bend, OR. September 25, 2014.
- University of Washington Comprehensive Oncology Review (5th Annual): "Germ cell tumors/testicular cancer." Seattle, WA. September 27, 2014.
- Seattle Cancer Care Alliance Network Physician Educational Outreach Program – Bozeman Deaconess Cancer Center: "Hot topics for prostate and bladder cancer." Bozeman, MT. October 14, 2014.
- Program in Prostate Cancer Research/SPORE: "Clinical experience with insulin-like growth factor receptor I (IGF-IR) inhibition in prostate cancer." Fred Hutchinson Cancer Research Center, Seattle, WA. October 30, 2014.
- Body Imaging Radiology Section Lecture Series: "Challenges in imaging of genitourinary malignancies." University of Washington Medical Center, Seattle, WA. November 12, 2014.
- Seattle Cancer Care Alliance Network Physician Educational Outreach Program – Spokane Valley Cancer Center: "The promise of immunotherapy for bladder cancer." Spokane, WA. November 13, 2014.
- Hematology/Oncology Fellows' Lecture Series: "Bladder cancer: a rapidly growing research arena." Fred Hutchinson Cancer Research Center, Seattle, WA. December 19, 2014.
- Oncology Grand Rounds: "Prostate cancer from the medical oncologist perspective…it's not all about castration-resistant disease." Fred Hutchinson Cancer Research Center, Seattle, WA. December 23, 2014.
- Us Too: "Timing and sequencing of therapeutic agents in metastatic prostate cancer." Greenwood Senior Center, Seattle, WA. March 25, 2015.
- Seattle Cancer Care Alliance Network Physician Educational Outreach Program – Tri Cities Cancer Center: "Metastatic prostate cancer therapeutic sequencing, combination and trials." Kennewick, WA. April 23, 2015.
- Seattle Cancer Care Alliance Network Physician Educational Outreach Program – The Vancouver Clinic: "Key therapeutic questions in metastatic prostate cancer." Vancouver, WA. May 5, 2015.
- Scripps 12th Annual Oncology Update: "Genitourinary cancer update." Seattle, WA. August 15, 2015.
- Flash Rounds: "Seven tips to developing a clinical research career." Fred Hutchinson Cancer Research Center. Seattle, WA. September 4, 2015.
- Genentech Educational Presentation: "Current challenges in managing bladder cancer." Seattle, WA. October 22, 2015.
- Hematology/Oncology Fellows' Lecture Series: "Germ cell tumors/testicular cancer." Fred Hutchinson Cancer Research Center. Seattle, WA. October 23, 2015.
- Fred Hutch Clinical Oncology Grand Rounds: "PET imaging in prostate cancer: Will it ever be more than a research tool?" Fred Hutchinson Cancer Research Center. Seattle, WA. January 12, 2016.

- Seattle Cancer Care Alliance Network Physician Educational Outreach Program – Bozeman Deaconess Cancer Center: "Urothelial carcinoma – Life after platinum." Bozeman, MT. May 20, 2016.
- Pacific NorthWest Prostate Cancer SPORE Retreat: "Clinical Core D." Fred Hutchinson Cancer Research Center, Seattle, WA. July 25, 2016.
- Genitourinary Oncology Staff Education Sessions: "ASCO 2016 prostate and bladder cancer updates." Seattle Cancer Care Alliance, Seattle, WA. August 11, 2016.
- Society for Immunotherapy of Cancer's (SITC) Advances in Cancer Immunotherapy – Washington Program: "Immunotherapy for genitourinary cancers." Seattle, WA. August 19, 2016.
- Remedica Medical Education and Publishing CME – Lecture to Seattle Cancer Care Alliance Advanced Practice Providers: "P3 – Patient selection and Practice in Prostate cancer." Seattle, WA. November 21, 2016.
- Providence Regional Medical Center: "P3 – Patient selection and Practice in Prostate cancer." Everett, WA. December 8, 2016.
- Remedica Medical Education and Publishing CME – Lecture to Fred Hutchinson Cancer Research Center Hematology/Oncology Fellows: "P3 – Patient selection and Practice in Prostate cancer." Seattle, WA. December 14, 2016.
- Seattle Cancer Care Alliance Educational Lecture: "Emerging immunotherapies and systemic therapies for metastatic urothelial carcinoma." Seatac, WA. March 1, 2017.
- 2016 6th Annual Institute of Prostate Cancer Research Symposium: "PET imaging in prostate cancer: Finding local recurrences and management of oligometastatic disease." Fred Hutchinson Cancer Research Center, Seattle, WA. March 18, 2017.
- Pacific NorthWest Prostate Cancer SPORE Retreat: "Clinical Core D." Fred Hutchinson Cancer Research Center, Seattle, WA. July 24, 2017.
- Seattle Genetics Lecture Series: "The evolving urothelial carcinoma landscape." Bothell, WA. August 4, 2017.
- University of Washington Comprehensive Hematology and Oncology Review (8th Annual): "Prostate cancer board review." Seattle, WA. September 25, 2017.
- Clinical Research Division: "Informed consent elements documentation." Fred Hutchinson Cancer Research Center, Seattle, WA. November 13, 2017.
- Medical Oncology Sections Meeting: "Informed consent elements documentation." Seattle Cancer Care Alliance, Seattle, WA. December 7, 2017.
- **University of Washington Medicine Grand Rounds: "Clinical research in prostate cancer." University of Washington School of Medicine, Seattle, WA. January 11, 2018.**
- Clinical Research Services, Fred Hutchinson Cancer Research Consortium: "Prostate cancer overview and impactful clinical research." Fred Hutchinson Cancer Research Center, Seattle, WA. January 11, 2018.
- Solid Tumor Conference, Fred Hutchinson Hematology-Oncology Fellowship Program: "GU boards review for fellows – Key points to remember." Fred Hutchinson Cancer Research Center, Seattle, WA. April 27, 2018.
- Institute for Prostate Cancer Research 2018 Symposium – Breakthroughs in prostate cancer research: "Prostate Cancer Tumor Board." Fred Hutchinson Cancer Research Center, Seattle, WA. April 28, 2018.
- External Advisory Board Meeting, Fred Hutchinson/University of Washington Cancer Consortium: "Clinical Protocol and Data Management." Fred Hutchinson Cancer Research Center, Seattle, WA. June 15, 2018.
- Oncology Grand Rounds: "Treatment intensification for castration-sensitive prostate cancer and management of oligometastatic disease." Fred Hutchinson Cancer Research Center, Seattle, WA. June 19, 2018.

- University of Washington Comprehensive Hematology and Oncology Review (9th Annual): "Prostate cancer board review." Seattle, WA. September 15, 2018.
- Genitourinary Oncology Staff Education Sessions: "Prostate cancer overview – clinical and research impact." Seattle Cancer Care Alliance, Seattle, WA. February 7, 2019.
- External Advisory Board Meeting, Fred Hutchinson/University of Washington Cancer Consortium: "Clinical Protocol and Data Management." Fred Hutchinson Cancer Research Center, Seattle, WA. March 8, 2019.
- Institute for Prostate Cancer Research 2019 Symposium – Breakthroughs in prostate cancer research: "Imaging in prostate cancer – state of the field." Fred Hutchinson Cancer Research Center, Seattle, WA. May 11, 2019.
- Program in Prostate Cancer Research/SPORE: "Implications of next generation PET imaging in prostate cancer." Fred Hutchinson Cancer Research Center, Seattle, WA. May 16, 2019.
- NCI Cancer Center Support Grant Site Visit: "Clinical drotocol and data management." Fred Hutchinson Cancer Research Center, Seattle, WA. May 29, 2019.
- 7th Annual International Conferences on Advances in Hematology and Oncology: "Bladder cancer updates from ASCO 2019." Seattle, WA. June 30, 2019.
- Seattle (Bellevue) UsToo: "Prostate cancer disease states and treatments." Bellevue, WA. July 15, 2019.
- Seattle (Bellevue) UsToo: "Next generation PET imaging in prostate cancer." Bellevue, WA. July 15, 2019.
- Medical Oncology Sections Meeting: "Genitourinary Medical Oncology (GUMO) research interests and updates." Seattle Cancer Care Alliance, Seattle, WA. August 1, 2019.
- Genitourinary Oncology Staff Education Sessions: "Immunotherapy for genitourinary cancers." Seattle Cancer Care Alliance, Seattle, WA. October 10, 2019.
- Institute of Prostate Cancer Research Development Lecture: "Proving the impact of next generation PET imaging in prostate cancer." Fred Hutchinson Cancer Research Center, Seattle, WA. October 17, 2019.
- Seattle Cancer Care Alliance NeuroEndocrine Tumor Board: "Iobenguane ^{131}I for the treatment of advanced neuroendocrine tumors that are norepinephrine transporter avid on imaging, in a multicenter, open-label phase 2 basket trial (FORESIGHT)." Seattle Cancer Care Alliance, Seattle, WA. December 20, 2019.
- Seattle UsToo: "The future impact of next generation PET imaging in prostate cancer." Seattle, WA. January 22, 2020.
- GU Medical Oncology Research Staff: "Recent updates in the last year for advanced prostate cancer." Fred Hutchinson Cancer Research Center, Seattle, WA. January 23, 2020.
- Curio Science – Community Opinions in Prostate Cancer: "Current and emerging therapies for practice with metastatic castration-sensitive prostate cancer." Seattle, WA. March 5, 2020.
- Medical Oncology Sections Meeting: "Clinical research updates – Learning from feedback on our competitive renewals and upcoming process improvments." Seattle Cancer Care Alliance, Seattle, WA. April 2, 2020.
- Lead Academic Performance Site National Clinical Trials Network Leadership Meeting: "NCTN Leadership Team introduction." Seattle Cancer Care Alliance, Seattle, WA. September 2, 2020.
- Medical Oncology Sections Meeting: "Clinical trials startup process improvements." Seattle Cancer Care Alliance, Seattle, WA. September 3, 2020.
- Genitourinary Leadership Committee Meeting: "Clinical trials startup process improvements – specific to Genitourinary Oncology." Seattle Cancer Care Alliance, Seattle, WA. October 20, 2020.

- Clinical Research Division Faculty Meeting: "Clinical trials startup process improvements – specific to CRD." Fred Hutchinson Cancer Research Center, Seattle, WA. November 2, 2020.
- Curio Science – Opinions in Bladder Cancer: "Treatment of metastatic urothelial cancer in the post-platinum, post-immunotherapy setting." Seattle, WA by Virtual Meeting. November 11, 2020.
- Institutional Perspectives in Cancer presented by OncLive: "Increasing awareness of nonmetastatic (M0) castration-resistant prostate cancer." Seattle, WA by Virtual Meeting. November 24, 2020.
- University of Washington Clinical Research Director Meeting: "Clinical trial start-up process improvements and challenges." Seattle, WA by Virtual Meeting. February 1, 2021.
- Seattle Cancer Care Alliance Board of Directors' Enrichment Series: "Paving the path forward with next generation PET imaging in prostate cancer." Seattle, WA by Virtual Meeting. February 22, 2021.
- Program in Prostate Cancer Research/SPORE: "Antibody drug conjugates in bladder cancer – reaching new targets." Fred Hutchinson Cancer Research Center, Seattle, WA. February 25, 2021.
- National Cancer Trials Network Leadership Committee Meeting: "Bi-annual Spring Meeting." Fred Hutchinson Cancer Research Center, Seattle, WA. March 26, 2021.
- University of Washington Clinical Research Director Meeting: "Race and ethnicity clinical trial accrual data." Seattle Cancer Care Alliance, Seattle, WA. May 3, 2021.
- Fred Hutchinson Cancer Research Consortium Institutional Review Board Diverse Enrollment Subcommittee: "Race and ethnicity clinical trial accrual data." Fred Hutchinson Cancer Research Center, Seattle, WA. May 14, 2021.
- Genitourinary Oncology Leadership Meeting: "Race and ethnicity clinical trial accrual data." Seattle Cancer Care Alliance, Seattle, WA. May 18, 2021.
- Fred Hutchinson Cancer Consortium Executive Committee: "Race and ethnicity clinical trial accrual data." Seattle Cancer Care Alliance, Seattle, WA. June 1, 2021.
- Institute for Prostate Cancer Research (IPCR) 2021 Symposium – Advanced prostate cancer: "PSMA-targeted therapy – The next big thing?" Fred Hutchinson Cancer Research Center, Seattle, WA. June 5, 2021.
- Targeted Oncology and HRA: "Case-based round table meeting on castration resistant prostate cancer." Virtual Meeting, Washington. June 15, 2021.
- 2021 Seattle Cancer Care Alliance Genitourinary Oncology Retreat: "Next generation imaging." Seattle, WA. June 17, 2021.
- 2021 Seattle Cancer Care Alliance Genitourinary Oncology Retreat: "Expanding research in the community – NCTN pilot." Seattle, WA. June 17, 2021.
- Seattle UsToo: "PSMA-targeted theranostics for prostate cancer." Virtual Meeting, Seattle, WA. July 28, 2021.
- Medical Oncology Sections Meeting: "Race and ethnicity clinical trial accrual data." Seattle Cancer Care Alliance, Seattle, WA. September 2, 2021.
- External Advisory Board Meeting, Fred Hutchinson/University of Washington Cancer Consortium: "Clinical Protocol and Data Management." Fred Hutchinson Cancer Research Center, Seattle, WA. September 27, 2021.
- National Cancer Trials Network Leadership Committee Meeting: "Bi-annual Virtual Fall Meeting." Fred Hutchinson Cancer Research Center, Seattle, WA. October 1, 2021.
- University of Washington and Fred Hutchinson Cancer Research Center Assistant Professors' Meeting: "Consortium trial startup and clinical trial process improvement." Fred Hutchinson Cancer Research Center, Seattle, WA. February 8, 2022.

- University of Washington and Fred Hutchinson Cancer Research Center Associate Professors' Meeting: "Consortium trial startup and clinical trial process improvement." Fred Hutchinson Cancer Research Center, Seattle, WA. March 1, 2022.
- University of Washington Internal Medicine Residency Program: "How to think about the PSA test and prostate cancer screening." March 18, 2022.
- External Advisory Board Meeting, Fred Hutchinson/University of Washington Cancer Consortium: "Clinical Research Overview and Clinical Protocol and Data Management." Fred Hutchinson Cancer Research Center, Seattle, WA. May 26, 2022.
- Curio Science Community Opinions – Opinions in Bladder Cancer, An Interactive Local Workshop: "Post-platinum or post immunotherapy, and subsequent therapy for locally advanced/metastatic urothelial carcinoma." Seattle, WA. August 31, 2022.
- Medical Oncology Sections Meeting: "Ongoing Genitourinary Medical Oncology (GUMO) clinical/translational research highlights." Fred Hutchinson Cancer Center, Seattle, WA. November 3, 2022.
- Fred Hutchinson Cancer Center Strategic Planning Meeting: "Clinical research updates from the lab to the bedside" Fred Hutchinson Cancer Center, Seattle, WA. November 4, 2022.
- Aptitude Health Live CASES: "Management of metastatic hormone sensitive prostate cancer." Seattle, WA. November 19, 2022.
- Aptitude Health Live CASES: "Management of metastatic castration resist prostate cancer." Seattle, WA. November 19, 2022.
- Aptitude Health Live CASES: "First-line therapy for advanced urothelial carcinoma." Seattle, WA. November 19, 2022.
- Aptitude Health Live CASES: "Second-line and subsequent management of advanced urothelial carcinoma." Seattle, WA. November 19, 2022.

INVITED SPEAKER NATIONAL/INTERNATIONAL

- Genentech, Inc.: "Retroviral RNA interference: systems development and biologic discoveries with telomerase." San Francisco, CA. April 6, 2004.
- **Stanford University Medical Center: "Retroviral RNA interference: systems development and biologic discoveries with telomerase." Stanford, CA. April 27, 2004.**
- **University of California Davis School of Medicine: "Retroviral RNA interference: systems development and biologic discoveries with telomerase." Sacramento, CA. April 30, 2004.**
- 8th Annual Western Hawaii Cancer Symposium: "Clinical implications of angiogenesis in solid tumor oncology." Kona, HI. September 10, 2005.
- Novartis Oncology: "Current issues in the treatment of bone metastases." Reno, NV. February 20, 2007.
- Novartis Oncology: "Treatment of solid tumor bone metastases with bisphosphonates." Anchorage, AK. June 13, 2007.
- Southwest Oncology Group Fall GU Committee Meeting: "Tissue inhibitor of metalloproteinase-1 (TIMP-1) as a prognostic and predictive biomarker for men receiving chemotherapy for hormone-refractory prostate cancer." Huntington Beach, CA. October 4, 2007.
- American Urologic Association Northeastern Section: "Emerging role of selective estrogen receptor modulators in prostate cancer." Santa Ana Pueblo, NM. September 20, 2008.
- American Urologic Association New England Section: "Emerging role of selective estrogen receptor modulators in prostate cancer." Rio Grande, Puerto Rico. September 26, 2008.
- **Prostate Cancer Foundation Scientific Symposium: "Prostate cancer bone metastasis biomarkers." Lake Tahoe, NV. October 16, 2008.**

- Southwest Oncology Group Spring GU Committee Meeting: "A phase 2 study of combined androgen deprivation and IMC-A12 for patients with new hormone-sensitive metastatic prostate cancer." San Francisco, CA. April 23, 2009.
- 12th Annual Western Hawaii Cancer Symposium: "Translational oncology in clinical practice." Kona, HI. September 4, 2009.
- **Prostate Cancer Research Institute (PCRI) 2009 Prostate Cancer Conference: "Reducing side effects of testosterone deprivation." Los Angeles, CA. September 12, 2009.**
- Southwest Oncology Group Fall GU Committee Meeting: "A randomized phase 2 study of combined androgen deprivation versus combined androgen deprivation and IMC-A12 for patients with new hormone-sensitive metastatic prostate cancer." Chicago, IL. October 24, 2009.
- Second Annual Roche Diagnostics Bone Metastatic Cancer Advisory Board: "Prognostic markers for metastatic bone disease in prostate cancer." Arlington, VA. October 29, 2009.
- Prostate Cancer Clinical Trials Consortium Annual Review: "Using metabolic imaging to assess response to therapy in prostate cancer bone metastases." Vienna, VA. November 18, 2009.
- Prostate Cancer Educational Council: "Beyond screening and diagnosis – utility of prostate specific antigen by disease state." Content Development Working Group Moderator. Philadelphia, PA. November 20, 2009.
- 10th Annual Meeting of the Society of Urologic Oncology: "Androgen deprivation therapy induced estrogen deficiency side effects." Bethesda, MD. December 4, 2009.
- Center for Biomedical Continuing Education: "Bone health across the cancer continuum: Updates and insight to an evolving story." Chicago, IL. February 9, 2010.
- Billings Clinic Tumor Board: "Bone health across the cancer continuum: Updates and insight to an evolving story." Billings, MT. March 30, 2010.
- Center for Biomedical Continuing Education: "Bone health across the cancer continuum: Updates and insight to an evolving story." New York, NY. April 8, 2010.
- Southwest Oncology Group Spring GU Committtee Meeting: "A randomized phase 2 study of combined androgen deprivation versus combined androgen deprivation and IMC-A12 for patients with new hormone-sensitive metastatic prostate cancer." San Francisco, CA. April 18, 2010.
- Mercy Regional Medical Center Grand Rounds: "Bone health across the cancer continuum: Updates and insight to an evolving story." Durango, CO. April 20, 2010.
- Sparrow Professional Building Grand Rounds: "Bone health across the cancer continuum: Updates and insight to an evolving story." Lansing, MI. April 30, 2010.
- **Education Session, Evolving Standards of Care in Metastatic Castration-resistant Prostate Cancer: "Bone directed therapy for prostate cancer: present standards and potential new options." 2010 American Society of Clinical Oncology, Chicago, IL. June 7, 2010.**
- **University of Texas Southwestern Combined Modality Conference: "Boning up with prostate cancer." Dallas, TX. July 2, 2010.**
- **Wayne State University / Karmanos Cancer Institute Prostate Cancer Working Group Conference: "Bone health in prostate cancer: The basics and some propaganda." Detroit, MI. August 20, 2010.**
- 13th Annual Western Hawaii Cancer Symposium: "Emerging new therapies for metastatic castration resistant prostate cancer." Kona, HI. September 4, 2010.
- South Texas Institute of Cancer: "Clinical debates in castration-refractory prostate cancer." Corpus Christi, TX. September 7, 2010.
- Texas Hematology/Oncology: "Clinical debates in castration-refractory prostate cancer." McKinney, TX. September 9, 2010.

- **Prostate Cancer Foundation Scientific Symposium: "Imaging prostate cancer bone metastases with sodium fluoride (NaF) PET." Washington, DC. September 16, 2010.**
- **City of Hope Oncology Grand Rounds: "Clinical decision making in castration-resistant prostate cancer." Duarte, CA. October 5, 2010.**
- Mount Clemens Regional Medical Center Oncology Grand Rounds: "Clinical debates in castration-refractory prostate cancer." Mount Clemens, MI. October 13, 2010.
- Great Falls Clinic Cancer Center: "Clinical debates in castration-refractory prostate cancer." Great Falls, MT. October 14, 2010.
- Southwest Oncology Group Fall GU Committee Meeting: "A randomized phase 2 study of combined androgen deprivation versus combined androgen deprivation and Cixutumumab (IMC-A12) for patients with new hormone-sensitive metastatic prostate cancer." Chicago, IL. October 23, 2010.
- Mercy Hospital: "Clinical debates in castration-refractory prostate cancer." Bakersfield, CA. November 3, 2010.
- **University of California San Diego Hematology/Oncology Grand Rounds: "Prostate Cancer: Honing in on the bones." San Diego, CA. January 14, 2011.**
- Southwest Oncology Group Spring GU Committee Meeting: "A randomized phase 2 study of combined androgen deprivation versus combined androgen deprivation and Cixutumumab (IMC-A12) for patients with new hormone-sensitive metastatic prostate cancer." San Francisco, CA. April 16, 2011.
- Providence Alaska Medical Center: "Advances in castration-resistant prostate cancer." Anchorage, AK. April 27, 2011.
- Bristol-Myers Squibb ASCO Dasatinib Investigator Initiated Trial Meeting: "Determining pharmacodynamic effects of Dasatinib on bone with ^{18}F-fluoride PET imaging in men with castration resistant prostate cancer." Chicago, IL. June 4, 2011.
- Millennium Pharmaceuticals, Inc. Prostate Cancer Update Educational Program: "Hormone-sensitive prostate cancer – recent updates and ongoing trials." Cambridge, MA. October 4, 2011.
- SWOG Fall GU Committee Meeting: "A randomized phase 2 study of combined androgen deprivation versus combined androgen deprivation and Cixutumumab (IMC-A12) for patients with new hormone-sensitive metastatic prostate cancer." San Antonio, TX. October 15, 2011.
- OncoGeneX OGX-427-02 Bladder Cancer Phase 2 Investigator Meeting: "A phase 1 trial of OGX-427, a 2-methoxyethyl antisense oligonucleotide against Heat Shock Protein 27." Scottsdale, AZ. November 5, 2011.
- **Yale Cancer Center NP Conference: "Prostate cancer: It's all about the bones." New Haven, CT. November 18, 2011.**
- **2012 Genitourinary Cancers Symposium, General Session II: Castrate Resistant Prostate Cancer – Treatment Sequencing and Implementation: "Novel targets, agents, and trials." San Francisco, CA. February 2, 2012.**
- **2012 Genitourinary Cancers Symposium, General Session II: Castrate Resistant Prostate Cancer – Treatment Sequencing and Implementation: "Case study and panel discussion." San Francisco, CA. February 2, 2012.**
- Prostate Cancer Skeletal Metastasis Workshop, Combined P01 Meeting: "Imaging response to therapy in prostate cancer bone metastases – PET as a biomarker." Ann Arbor, MI. April 12, 2012.
- SWOG Spring GU Committee Meeting: "A randomized phase 2 study of combined androgen deprivation versus combined androgen deprivation and Cixutumumab (IMC-A12) for patients with new hormone-sensitive metastatic prostate cancer." San Francisco, CA. April 14, 2012.

- Astellas Pharma Medical Science Liaison Education Lecture: "The dynamic treatment landscape for castration-resistant prostate cancer." Internet lecture. May 4, 2012.
- **Vanderbilt University: "Dem bones, dem bones, dem prostate cancer bones." Nashville, TN. May 17, 2012.**
- **Genitourinary (Prostate) Cancer Poster Discussion Session: "Sex, Drugs, and Bones." 2012 American Society of Clinical Oncology, Chicago, IL. June 4, 2012.**
- Dendreon Advisory Meeting: "The oncologist's perspective of Provenge for patients with asymptomatic/minimally symptomatic metastatic castrate-resistant prostate cancer." San Diego, CA. June 15, 2012.
- Dendreon Oncology Summit Advisory Board: "Provenge and the evolving treatment landscape for advanced prostate cancer." San Francisco, CA. June 23, 2012.
- Dendreon Oncology Summit Advisory Board: "Sequencing metastatic castration-resistant prostate cancer treatments of the future." San Francisco, CA. June 23, 2012.
- **University of California Davis 13th Annual Advances in Oncology 2012: "New therapeutic options in advanced castration-resistant prostate cancer." Sacramento, CA. September 22, 2012.**
- SWOG Fall Prostate Cancer Organ Site Meeting: "A randomized phase 2-3 trial of intermittent androgen deprivation therapy using Enzalutamide with a GnRH agonist versus Bicalutamide with a GnRH agonist in patients with non-metastatic castration-sensitive prostate cancer." Chicago, IL. October 19 and 20, 2012.
- SWOG Fall GU Committee Meeting: "A randomized phase 2 study of combined androgen deprivation versus combined androgen deprivation and Cixutumumab (IMC-A12) for patients with new hormone-sensitive metastatic prostate cancer." Chicago, IL. October 20, 2012.
- South Texas Comprehensive Cancer Center: "Optimizing care for patients with advanced prostate cancer: evolving targets and emerging treatment paradigms." Corpus Christi, TX. December 4, 2012.
- Hoag Memorial Hospital Oncology Grand Rounds: "Optimizing care for patients with advanced prostate cancer: evolving targets and emerging treatment paradigms." Newport Beach, CA. February 28, 2013.
- Dendreon Oncology Advisory Board Meeting: "Sipuleucel-T and its use in community-based oncology practices." Washington, DC. April 18, 2013.
- SWOG Spring GU Committee Meeting: "A randomized phase 2 study of combined androgen deprivation versus combined androgen deprivation and Cixutumumab (IMC-A12) for patients with new hormone-sensitive metastatic prostate cancer." San Francisco, CA. May 2, 2013.
- Medivation Preclinical ASCO Advisory Board Meeting: "The role of SRC in prostate cancer – are there still potential clinical implications?" Chicago, IL. May 30, 2013.
- Dendreon Medical Oncologist Advisory Board: "Early detection of metastatic castration-resistant prostate cancer." Chicago, IL. May 31, 2013.
- Dendreon Medical Oncologist Advisory Board: "Metastatic castration-resistant prostate cancer, a changing landscape." Chicago, IL. May 31, 2013.
- **Genitourinary (Prostate) Cancer Poster Discussion Session: "Prognosis and predication of outcomes in castration-resistant prostate cancer." 2013 American Society of Clinical Oncology, Chicago, IL. June 1, 2013.**
- Janssen Post-ASCO Educational Update Meeting: "Updates on metastatic castration-resistant prostate cancer studies from ASCO 2013." Chicago, IL. June 4, 2013.
- Dendreon: "Cancer immunotherapy – fundamental concepts and emerging role." Las Vegas, NV. July 25, 2013.
- Challenging Cases in Oncology powered by Xcenda: "Case 6 – Advanced prostate cancer prognosis and treatment." Las Vegas, NV. July 27, 2013.

- Challenging Cases in Oncology powered by Xcenda: "Prostate cancer debrief." Las Vegas, NV. July 27, 2013.
- Compass Oncology 2013 Comprehensive Cancer Network: "Integration of novel management strategies for castrate-resistant prostate cancer." Portland, OR. September 19, 2013.
- Abilene Regional Medical Center 2013 Comprehensive Cancer Network: "Integration of novel management strategies for castrate-resistant prostate cancer." Abilene, TX. September 24, 2013.
- Mercy Medical Center 2013 Comprehensive Cancer Network: "Integration of novel management strategies for castrate-resistant prostate cancer." Canton, OH. October 4, 2013.
- SWOG Fall Prostate Cancer Organ Site Meeting: "A randomized phase 2-3 trial of intermittent androgen deprivation therapy using Enzalutamide with a GnRH agonist versus a GnRH agonist alone in patients with non-metastatic castration-sensitive prostate cancer." Chicago, IL. October 11, 2013.
- SWOG Fall GU Committee Meeting: "A randomized phase 2 study of combined androgen deprivation versus combined androgen deprivation and Cixutumumab (IMC-A12) for patients with new hormone-sensitive metastatic prostate cancer." Chicago, IL. October 11, 2013.
- Myriad Genetics and Laboratories: "Prostate cancer/Prolaris medical oncology advisory board meeting." Salt Lake City, UT. October 19, 2013.
- **18th Brazilian Oncology Conference: "Post-ADT phase 3 clinical evidence: Efficacy of abiraterone acetate." Brasilia, Brazil. October 23, 2013.**
- Janssen Dinner Launch: "Metastatic castration-resistant prostate cancer cases." Brasilia, Brazil. October 24, 2013.
- **Chemotherapy Foundation Symposium: "Novel PET imaging in prostate cancer." New York City, NY. November 8, 2013.**
- St. Lukes Mountain States Tumor Institute 2013 Comprehensive Cancer Network: "Integration of novel management strategies for castrate-resistant prostate cancer." Boise, ID. November 13, 2013.
- Bergan Mercy Medical Center 2013 Comprehensive Cancer Network: "Integration of novel management strategies for castrate-resistant prostate cancer." Omaha, NE. November 20, 2013.
- Medivation Incorporated: "A randomized phase 2-3 trial of intermittent androgen deprivation therapy using enzalutamide with a GnRH agonist versus a GnRH agonist alone in patients with non-metastatic castration-sensitive prostate cancer." San Francisco, CA. November 22, 2013.
- Elsevier Urology Round Table: "Measuring immune response in men with metastatic castration-resistant prostate cancer." Washington, DC. December 7, 2013.
- Dendreon: "Cancer immunotherapy – fundamental concepts and emerging role." Santa Barbara, CA. December 19, 2013.
- Hoag Memorial Hospital Oncology Grand Rounds: "Integration of novel management strategies for castrate-resistant prostate cancer." Newport Beach, CA. January 23, 2014.
- Dendreon Medical Oncologist Advisory Board: "Cancer immunotherapy – fundamental concepts and emerging role." Santa Barbara, CA. February 6, 2014.
- Dendreon: "Cancer immunotherapy – fundamental concepts and emerging role." Honolulu, HI. February 19, 2014.
- **7th Annual IntraSPORE Prostate Cancer Program Retreat: "Prostate cancer and the clinical sciences – where are we and what we need to do?" Fort Lauderdale, FL. March 17, 2014.**
- St. Lukes Mountain States Tumor Institute: "Overcoming cancer immunoevasion: the role of immunotherapy." Boise, ID. April 3, 2014.
- Dendreon: "Overcoming cancer immunoevasion: the role of immunotherapy." Billings, MT. April 22, 2014.

- SWOG Spring GU Organ Site Working Group Meeting: "A randomized phase 2 study of combined androgen deprivation versus combined androgen deprivation and Cixutumumab (IMC-A12) for patients with new hormone-sensitive metastatic prostate cancer." San Francisco, CA. May 1, 2014.
- Dendreon Junior Faculty ASCO Advisory Meeting: "A new era of immunotherapy in treating prostate cancer." Chicago, IL. May 29, 2014.
- Janssen Post-ASCO 2014 Educational Update Meeting: "Developments in initial treatment approaches for advanced prostate cancer." Chicago, IL. June 3, 2014.
- Dendreon Sales Training Workshop: "Health care provider training for clinical proficiency." Atlanta, GA. June 18, 2014.
- Enzalutamide Medical Advisory Board: "Current clinical practice landscape incorporating ASCO 2014 data and upcoming key clinical trials in prostate cancer." New York, NY. July 26, 2014.
- **Best of ASCO 2014: "Prostate cancer 2014 – Progress! Not progression." Seattle, WA. August 23, 2014.**
- Meet the Expert for Zytiga – a community forum: "The metastatic castration-resistant prostate cancer treatment paradigm: more choices, more questions." Yokohama, Japan. August 27, 2014.
- **52nd Annual Meeting of Japanese Society of Clinical Oncology: "The metastatic castration-resistant prostate cancer treatment paradigm: more choices, more questions." Yokohama, Japan. August 28, 2014.**
- Meet the Expert for Castration-Resistant Prostate Cancer – an academician forum: "The metastatic castration-resistant prostate cancer treatment paradigm: more choices, more questions." Yokohama, Japan. August 29, 2014.
- Challenging Cases in Prostate Cancer powered by Xcenda: "The metastatic castration-resistant prostate cancer smorgasbord." Las Vegas, NV. September 19, 2014.
- Regional Summit on Practical and Emerging Agents in Prostate Cancer: "Immunotherapy approaches to prostate cancer." New York, NY. October 4, 2014.
- **15th Annual Meeting of the Society of Urologic Oncology: "Prostate cancer sequencing prior to chemotherapy." Bethesda, MA. December 5, 2014.**
- **University of Chicago: "Immunotherapy for genitourinary malignancies." Chicago, IL. December 18, 2014.**
- Elmhurst Memorial Clinic: "Overcoming cancer immunoevasion: the role of immunotherapy." Elmhurst, IL. December 18, 2014.
- Tolmar Advisory Council Meeting: "Maximal castration for advanced prostate cancer? Correlations between testosterone levels and outcomes." San Diego, CA. January 9, 2015.
- Regional Summit on Practical and Emerging Agents in Prostate Cancer: "Sipuleucel-T: Current status and optimal patient selection." Dallas, TX. January 17, 2015.
- Rocky Mountain Cancer Center Boulder: "Overcoming cancer immunoevasion: the role of immunotherapy." Boulder, CO. February 5, 2015.
- Dendreon: "Overcoming cancer immunoevasion: the role of immunotherapy." Denver, CO. February 5, 2015.
- The Urology Center of Colorado: "Immunotherapy for bladder cancer." Denver, CO. February 6, 2015.
- **2015 Genitourinary Cancers Symposium, General Session II: Evolving role of multimodality treatment in low volume hormone-sensitive metastatic disease: "Selection of systemic therapy: Chemotherapy and androgen axis agents." Orlando, FL. February 26, 2015.**
- PeerView Live CME: Clinical challenges in castration-resistant prostate cancer - How to choose the right treatment for the right patient at the right time: "Current and future directions with hormone therapy in prostate cancer." Orlando, FL. February 27, 2015.

- **University of Texas Houston: "Overcoming cancer immunoevasion: the role of immunotherapy." Houston, TX. March 16, 2015.**
- **University of Arizona Oncology Grand Rounds: "Clinical research in prostate cancer – exploring the castration-sensitive disease state." Tucson, AZ. March 27, 2015.**
- Genentech Bladder Cancer Steering Committee: "Urothelial bladder cancer disease states education." Dallas, TX. April 17, 2015.
- Dendreon Advisory Meeting – Integrating Leading-Edge Data Into Prostate Cancer Treatment and Research: "Impact of recent data on treatment considerations in prostate cancer: Resistance to androgen-targeted agents." Chicago, IL. May 28, 2015.
- Dendreon Advisory Meeting – Integrating Leading-Edge Data Into Prostate Cancer Treatment and Research: "Antigen spread following sipuleucel-T treatment." Chicago, IL. May 28, 2015.
- Peerview Live CME – Applying the Latest Evidence to Treatment Decisions in CRPC: Real Cases, Difficult Choices – You Make the Call: "Management options for previously treated metastatic CRPC: Latest data and considerations." Chicago, IL. May 29, 2015.
- Urologic Oncology Summit: "Castration-resistant prostate cancer: Biology and definitions." Panama City, Panama. June 27, 2015.
- Urologic Oncology Summit: "An overview of non-metastatic (M0) castration-resistant prostate cancer." Panama City, Panama. June 27, 2015.
- Urologic Oncology Summit: "Placing the evidence together in metastatic castration-resistant prostate cancer: Sequencing, combination?" Panama City, Panama. June 27, 2015.
- Urologic Oncology Summit: "Panel discussion: Special clinical scenarios for advanced prostate cancer." Panama City, Panama. June 27, 2015.
- Urologic Oncology Summit: "Role of docetaxel in the management of castration-sensitive prostate cancer." Panama City, Panama. June 27, 2015.
- 6th International Pacrim Breast and Prostate Cancer Meeting: PET imaging in prostate cancer: Research tool of standard clinical practice?" Stevenson, WA. July 21, 2015.
- Enzalutamide Medical Advisory Board: "ASCO 2015 data review." New York, NY. July 31, 2015.
- 3rd Annual International Conferences on Advances in Hematology and Oncology: "Metastatic prostate cancer – Management in the era of novel agents." Coeur d'Alene, ID. August 29, 2015.
- Genentech Educational Presentation: "The PD-L1 pathway in cancer immune evasion." Portland, OR. November 10, 2015.
- Janssen West Community Oncology Advisory Board Meeting: "Data review of abiraterone and enzalutamide, clinical sequencing and future directions in prostate cancer." Los Angeles, CA. November 11, 2015.
- **16th Annual Meeting of the Society of Urologic Oncology: "Clinical implications of genomics in treating prostate cancer." Washington, DC. December 3, 2015.**
- Merck Genitourinary Oncology Global Advisory Board Meeting: "Current treatment options for metastatic castration-resistant prostate cancer and potential role for checkpoint inhibitors in the future." Barcelona, Spain. January 29, 2016.
- Merck Genitourinary Oncology Global Advisory Board Meeting: "Update on checkpoint inhibitor data in bladder cancer." Barcelona, Spain. January 29, 2016.
- Genentech Educational Presentation: "The PD-L1 pathway in cancer immune evasion." Irvine, CA. March 10, 2016.
- Genentech Educational Presentation: "The PD-L1 pathway in cancer immune evasion." Anchorage, AK. March 16, 2016.
- Genentech Educational Presentation: "The PD-L1 pathway in cancer immune evasion." Phoenix, AZ. March 24, 2016.

- Florida Society of Clinical Oncology (FLASCO) Spring Session: "Sequencing agents in metastatic prostate cancer." Kissimmee, FL. April 9, 2016.
- Seattle Cancer Care Alliance 1st Comprehensive Cancer Update: "Treatment decision making for patients with metastatic prostate cancer." Honolulu, HI. April 16, 2016.
- Seattle Cancer Care Alliance 1st Comprehensive Cancer Update: "Bladder cancer – Major advancements coming soon." Honolulu, HI. April 16, 2016.
- Seattle Cancer Care Alliance 1st Comprehensive Cancer Update: "Testicular cancer – Winning the ball game." Honolulu, HI. April 16, 2016.
- Bayer West Area Meeting: "Metastatic castration-resistant prostate cancer overview." Phoenix, AZ. April 28, 2016.
- Genentech Educational Presentation: "The PD-L1 pathway in cancer immune evasion." Oxnard, CA. May 24, 2016.
- Bayer Corporation: "Post-ASCO 2016 Point of View." Global Webex. June 23, 2016.
- 4th Annual Canadian Urological Association and Canadian Urologic Oncology Group Multidisciplinary Meeting: "The promise of checkpoint inhibitors in urothelial cancer." Vancouver, BC, Canada. June 25, 2016.
- Janssen Medical Oncology Advisory Board: "Janssen oncology clinical development program in genitourinary malignancies." Chicago, IL. July 14, 2016.
- Genentech Lung and Urothelial Cancer Advisory Board: "Atezolizumab in urothelial cancer." Seattle, WA. July 16, 2016.
- **Best of ASCO 2016: "Genitourinary (Non-prostate) Cancer." San Diego, CA. August 13, 2016.**
- 4th Annual International Conferences on Advances in Hematology and Oncology: "Choices and decisions in metastatic prostate cancer." Coeur d'Alene, ID. August 14, 2016.
- **American Urological Association Advanced Prostate Cancer: Managing the Spectrum of Disease Symposium: "Comorbidities and side effect profiles: Considerations for various castration-resistant prostate cancer therapeutic strategies." Chicago, IL. September 24, 2016.**
- Merck KEYNOTE-365 Investigator Meeting: "Metastatic castration-resistant prostate cancer overview, current treatment and future directions." Baltimore, MD. October 20, 2016.
- 3rd Annual Summit on Genitourinary Malignancies: "Identifying prostate cancer patients for immunotherapy approaches." New York, NY. October 23, 2016.
- prIME Oncology, 2nd Annual West Cancer Center Oncology Conference, Collaboration for the Future Cure – Precision Medicine and Immuno-Oncology: "Immunotherapy in genitourinary cancers: The new frontier." Memphis, TN. November 18, 2016.
- **17th Annual Meeting of the Society of Urologic Oncology: "Immunotherapy for prostate cancer: What is the way forward?" San Antonio, TX. December 2, 2016.**
- **American Urological Association Advanced Prostate Cancer: Managing the Spectrum of Disease Symposium: "Comorbidities and side effect profiles: Considerations for various castration-resistant prostate cancer therapeutic strategies." Washington, DC. December 10, 2016.**
- **Society of Government Service Urologists – 2017 Kimbrough Urological Seminar: "Considerations for the symptomatic metastatic castration resistant prostate cancer patient: Beyond Abiraterone and Enzalutamide." San Diego, CA. January 14, 2017.**
- Annenberg Center for Health Sciences CME: Experts in Residence – "Bridging the gap from knowledge to practice in castration-resistant prostate cancer." Cancer Treatment Centers of America, Zion, IL. January 27, 2017.
- St. Lukes Mountain States Tumor Institute - Remedica Medical Education and Publishing CME: "P3 – Patient selection and Practice in Prostate cancer." Boise, ID. February 7, 2017.

- Targeted Oncology Case-Based Peer Perspectives: "Immunotherapy in advanced bladder cancer." Orlando, FL. February 24, 2017.
- Annenberg Center for Health Sciences CME: Experts in Residence – "Bridging the gap from knowledge to practice in castration-resistant prostate cancer." Beaumont Hospital, Royal Oak, MI. March 7, 2017.
- Annenberg Center for Health Sciences CME: Experts in Residence – "Bridging the gap from knowledge to practice in castration-resistant prostate cancer." Summerlin Hospital, Las Vegas, NV. March 14, 2017.
- Bayer Pharmaceuticals - Meet the Professor: "Overview of data related to sequential use of novel hormonal therapies in metastatic castration-resistant prostate cancer." Hanover, NJ. March 24, 2017.
- Hawaii Pacific Health - Remedica Medical Education and Publishing CME: "P3 – Patient selection and Practice in Prostate cancer." Honolulu, HI. April 10, 2017.
- SWOG Spring GU Organ Site Working Group Meeting: "Combination immune-oncology therapeutics in metastatic castration-resistant prostate cancer." San Francisco, CA. April 28, 2017.
- **American Urological Association 2017 Castration-Resistant Prostate Cancer Live Forum for Residents & Fellows: "Role of chemotherapy for metastatic castration-resistant prostate cancer." Boston, MA. May 11, 2017.**
- **PROSPECT 2017 Symposium Keynote Presentation: "What's hot in advanced prostate cancer today?" Melbourne, Australia. May 19, 2017.**
- **PROSPECT 2017 Symposium Diagnosis, Staging and Management of Locally Advanced Prostate Cancer: "Advances in imaging and implications for treatment of oligometastatic disease." Melbourne, Australia. May 20, 2017.**
- **PROSPECT 2017 Symposium Sequencing in Advanced Prostate Cancer – Current Therapies: "Therapeutic sequencing in metastatic castration-resistant prostate cancer." Melbourne, Australia. May 20, 2017.**
- **PROSPECT 2017 Symposium Rapid Fire Multidisciplinary Cases: "Case – sequencing in metastatic castration-resistant prostate cancer." Melbourne, Australia. May 20, 2017.**
- **PROSPECT 2017 Symposium A Look to the Future – Personalised and Supportive Care in Advanced Prostate Cancer: "High-risk non-metastatic (M0) castration-resistant prostate cancer – an evolving landscape." Melbourne, Australia. May 20, 2017.**
- Denali Oncology Group's 34th Educational Program Oncology in the Last Frontier: "Comorbidities and side effects and their effect on how we use therapeutic agents for advanced prostate cancer." Barrow, AK. June 24, 2017.
- Denali Oncology Group's 34th Educational Program Oncology in the Last Frontier: "Considerations with next generation sequencing results and precision medicine in prostate cancer." Barrow, AK. June 24, 2017.
- Bozeman Health - Remedica Medical Education and Publishing CME: "P3 – Patient selection and Practice in Prostate cancer." Bozeman, MT. July 6, 2017.
- 5th Annual International Conferences on Advances in Hematology and Oncology: "Metastatic prostate cancer: How to sequence newer agents." Coeur d'Alene, ID. August 12, 2017.
- 18th Future Directions in Urology Symposium: "Updates on use of radiopharmaceuticals in prostate cancer clinical trials." Colorado Springs, CO. August 22, 2017.
- **American Urological Association 2017 Castration-Resistant Prostate Cancer Live Forum for Residents & Fellows: "Role of chemotherapy for metastatic prostate cancer." Dallas, TX. September 9, 2017.**
- **American Urological Association Practical Management of Metastatic Prostate Cancer: Guidelines and Beyond: "Comorbidities and side effect profiles: Considerations for various**

castration-resistant prostate cancer therapeutic strategies." Dallas, TX. September 10, 2017.

- **American Urological Association Practical Management of Metastatic Prostate Cancer: Guidelines and Beyond: "Future directions in systemic therapy for prostate cancer." Dallas, TX. September 10, 2017.**
- **University of Utah/Huntsman Cancer Institute - Remedica Medical Education and Publishing CME: "P3 – Patient selection and Practice in Prostate cancer." Salt Lake City, UT. September 28, 2017.**
- Urological Oncology Committee of Taiwan Urological Association Preceptorship: "Novel therapies for the management of advanced prostate cancer." Taipei, Taiwan. October 14, 2017.
- Bayer Taiwan and Southeast Asia Advisory Meeting: "Real life experience with Radium-223 and new clinical evidence." Taipei, Taiwan. October 15, 2017.
- Bayer Taiwan and Southeast Asia Advisory Meeting: "Insights from evaluation criteria to treatment outcomes of Radium-223." Taipei, Taiwan. October 15, 2017.
- **American Urological Association 2017 Castration-Resistant Prostate Cancer Live Forum for Residents & Fellows: "Role of chemotherapy for metastatic prostate cancer." Los Angeles, CA. October 28, 2017.**
- **American Urological Association Practical Management of Metastatic Prostate Cancer: Guidelines and Beyond: "Comorbidities and side effect profiles: Considerations for various castration-resistant prostate cancer therapeutic strategies." Los Angeles, CA. October 29, 2017.**
- **American Urological Association Practical Management of Metastatic Prostate Cancer: Guidelines and Beyond: "Future directions in systemic therapy for prostate cancer." Los Angelese, CA. October 29, 2017.**
- Cancer Immunotherapy Trials Network Annual Meeting: "A randomized phase 2 study of atezolizumab plus recombinant human IL-7 (CYT107) in patients with locally advanced or metastatic urothelial carcinoma." National Harbor, MD. November 9, 2017.
- Remedica Medical Education and Publishing CME: "P3 – Patient selection and Practice in Prostate cancer." Summerlin Hospital, Las Vegas, NV. November 27, 2017.
- Purdue University PeerView CME: "Candid conversations in prostate cancer: State of the science and implications for improving patient care and outcomes." VA Southern Nevada Health Care System, Las Vegas, NV. December 19, 2017.
- Annenberg Center for Health Sciences CME: "Optimizing patient outcomes in castration-resistant prostate cancer: Moving urologists from knowledge to action." Holy Cross Hospital (Sinai Health System), Chicago, IL. February 28, 2018.
- Merck/MSD Prostate Cancer Global Advisory Board: "PARP inhibition and DNA repair deficiency in metastatic castration-resistant prostate cancer." San Francisco, CA. May 17, 2018.
- **Society for Basic Urology Research (SBUR)/Suociety of Urologic Oncology (SUO) Joint Meeting at the American Urological Association Annual Meeting: "Treatment of cisplatin-ineligible muscle-invasive bladder cancer patients." San Francisco, CA. May 19, 2018.**
- Onclive 2018 State of the Science: Genitourinary Cancers: "Treatment intensification for castration-sensitive prostate cancer." Salt Lake City, UT. May 24, 2018.
- **Huntsman Cancer Institute Genitourinary Oncology Symposium:** "Future of immuno-oncology in prostate cancer." Huntsman Cancer Institute/University of Utah, Salt Lake City, UT. May 25, 2018.
- Peerview Live CME – Newest Advances and Strategies in Prostate Cancer – Science and Stories on the Evolving Treatment Landscape and Implications for Patient Cancer: "DNA repair deficiency and implications for men with prostate cancer." Chicago, IL. June 1, 2018.

- **Education Session, Role of Precision Therapy in the Treatment of Advanced Urothelial Cancer: "Targeted therapies in advanced urothelial cancer." 2018 American Society of Clinical Oncology, Chicago, IL. June 4, 2018.**
- Annenberg Center for Health Sciences CME: "Optimizing patient outcomes in castration-resistant prostate cancer: Moving urologists from knowledge to action." North Side Hospital, Atlanta, GA. June 14, 2018.
- 6th Annual International Conferences on Advances in Hematology and Oncology: "Prostate cancer: Optimizing the use of newer agents." Coeur d'Alene, ID. August 5, 2018.
- 19th Future Directions in Urology Symposium: "Next generation anti-androgen therapies." Colorado Springs, CO. August 13, 2018.
- 19th Future Directions in Urology Symposium: "Next generation advanced and endocrine refractory prostate cancer." Colorado Springs, CO. August 14, 2018.
- Prostate Cancer Research Institute (PCRI) 2018 Prostate Cancer Patient Conference: "Pills, immune boosters & radiopharmaceuticals for prostate cancer treatment: Who, Where, When, How and Now?!" Los Angeles, CA. September 8, 2018.
- Singapore Urological Association: "Targeted alpha therapy in metastatic castration-resistant prostate cancer: Dawn or Dusk" Singapore. September 25, 2018.
- Asia-Pacific Metastatic Castration-Resistant Prostate Cancer Expert Exchange Summit: "Optimizing survival in metastatic castration-resistant prostate cancer: Radium-223 and its place in treatment plans: Clinician's perspective." National Cancer Center, Singapore. September 26, 2018.
- National University Hospital: "Targeted alpha therapy in metastatic castration-resistant prostate cancer: Dawn or Dusk" Singapore. September 27, 2018.
- Prostate Cancer Academy: "Role of androgen receptor blockers in advanced prostate cancer." Los Angeles, CA. October 13, 2018.
- Prostate Cancer Academy: "Role of chemotherapy and radiopharmaceuticals in the management and treatment of advanced prostate cancer." Los Angeles, CA. October 13, 2018.
- ESMO Satellite Symposium – Checkpoint inhibition in the treatment of cancer: Building the new standard of care across multiple solid tumors: "Checkpoint inhibition for the treatment of genitourinary cancers." Munich, Germany. October 19, 2018.
- Cancer Immunotherapy Trials Network Annual Meeting: "A randomized phase 2 study of atezolizumab plus recombinant human IL-7 (CYT107) in patients with locally advanced or metastatic urothelial carcinoma." Washington, DC. November 7, 2018.
- Windsor Regional Cancer Centre: "Integrating immune-oncology within the current treatment of advanced urothelial carcinoma." Windsor, ON, Canada. November 13, 2018.
- Ottowa Dinner Round: "Integrating immune-oncology within the current treatment of advanced urothelial carcinoma." Ottowa, ON, Canada. November 13, 2018.
- **Juravinski Cancer Centre Grand Rounds: "Integrating immune-oncology within the current treatment of advanced urothelial carcinoma." Hamilton, ON, Canada. November 14, 2018.**
- Sherbrooke Dinner Rounds: "Integrating immune-oncology within the current treatment of advanced urothelial carcinoma." Montreal, QC, Canada. November 14, 2018.
- **Princess Margaret Cancer Centre Grand Rounds: "Integrating immune-oncology within the current treatment of advanced urothelial carcinoma." Toronto, ON, Canada. November 15, 2018.**
- Greater Toronto Area Dinner Rounds: "Integrating immune-oncology within the current treatment of advanced urothelial carcinoma." Etobicoke, ON, Canada. November 15, 2018.

- Radium-223 dichloride Oncology Hospital Advisory Board: Management and unmet needs in metastatic castration-resistant prostate cancer: Radium-223 new clinical trials data. Dallas, TX. December 8, 2018.
- Peerview Live CME – Unraveling the Complexities of Prostate Cancer Management – Focus on Therapeutic Decisions for Early-Stage Disease and the Implications for Later-Stage Disease: "Androgen-targeting therapy in nonmetastatic (M0) castration-resistant prostate cancer." San Francisco, CA. February 15, 2019.
- **44th Annual UCLA State of the Art Urology Conference: "Late breaking news – treatment of oligometastatic prostate cancer." Marina Del Rey, CA. March 9, 2019.**
- **44th Annual UCLA State of the Art Urology Conference: "Pragmatic sequencing therapy for castrate resistant prostate cancer." Marina Del Rey, CA. March 9, 2019.**
- **44th Annual UCLA State of the Art Urology Conference: "Making the immune system work for the urologist." Marina Del Rey, CA. March 9, 2019.**
- Enfortumab Vedotin Community Advisory Board: "Metastatic urothelial cancer community patient profile." Dallas, TX. March 15, 2019.
- Enfortumab Vedotin Community Advisory Board: "Potential future treatment options for metastatic urothelial carcinoma." Dallas, TX. March 15, 2019.
- **Food & Drug Administration Mini-Symposium on Pathologic Complete Response in Bladder Cancer: "Clinical restaging in muscle-invasive bladder cancer – How do we do it and what does it mean?"** Silver Spring, MD. March 27, 2019.
- Annenberg Center for Health Sciences CME: "Optimizing patient outcomes in castration-resistant prostate cancer: Moving urologists from knowledge to action." Eisenhower Medical Center, Rancho Mirage, CA. March 28, 2019.
- Bayer Pharmaceuticals - Meet the Professor: "Earlier use of novel hormones for advanced prostate cancer and impact on the metastatic castration-resistant prostate cancer population." Hanover, NJ. April 4, 2019.
- Merck Pharmaceuticals – Prostate Program Phase III Studies Investigator Meeting Series: "KEYNOTE-365 Cohort A: Pembrolizumab plus olaparib in docetaxel-pretreated patients with metastatic castrate-resistant prostate cancer." Jersey City, NJ. April 12, 2019.
- **American Urological Association 2019 Evolving Role of the Urologist in Metastatic and Castration Resistant Prostate Cancer: A Guidelines and Case-Based Discussion: "Role of chemotherapy, treatment sequencing and future approaches." Chicago, IL. May 2, 2019.**
- Peerview Live CME – New Concepts in Prostate Cancer – What Oncologists Need to Know to Optimize Patient Outcomes: "Non-metastatic castration resistant prostate cancer." Chicago, IL. June 1, 2019.
- **Education Session Genitourinary (Non-prostate) Cancer – Formidable Scenarios in Urothelial and Variant Cancers of the Urinary Tract: "Cisplatin-ineligible patients with urothelial carcinoma – medical oncology perspective." 2019 American Society of Clinical Oncology Annual Meeting. Chicago, IL. June 2, 2019.**
- Washington State Urology Association Annual Conference: "Unraveling the complex treatment landscape of prostate cancer – Guidance for delivering evidence-based, patient-centered care." Leavenworth, WA. June 22, 2019.
- ASCO Direct Highlights – 2019 Official Annual Meeting Review: "Genitourinary cancers – The advances continue." New York, NY. July 19, 2019.
- FDA – Bladder Cancer Advocacy Network Workshop: "Clinical restaging in muscle-invasive bladder cancer – How do we do it and what does it mean?" Washington, DC. August 8, 2019.
- Clovis Prostate Cancer Clinical Immersion: "Biochemically-recurrent prostate cancer and implifcations of next generation PET imaging." Boulder, CO. August 27, 2019.

- Clovis Prostate Cancer Clinical Immersion: "Advanced prostate cancer and treatment sequencing." Boulder, CO. August 27, 2019.
- Clovis Prostate Cancer Clinical Immersion: "Prostate cancer biology, mechanisms of castration-resistance and drug-resistance." Boulder, CO. August 27, 2019.
- Prostate Cancer Academy: "Role of androgen receptor blockers in advanced prostate cancer." Los Angeles, CA. September 21, 2019.
- Prostate Cancer Academy: "Role of chemotherapy and radiopharmaceuticals in the management and treatment of advanced prostate cancer." Los Angeles, CA. September 21, 2019.
- GU Connect Face to Face Meeting at ESMO 2019: "GU Connect educational focus and priorities 2020." Barcelona, Spain. September 28, 2019.
- Janssen Advisory Board 2019 Meeting: "Current approach and treatment patterns in metastatic castration sensitive prostate cancer." San Francisco, CA. October 12, 2019.
- Targeted Oncology and HRA: "Case-based perspectives in prostate cancer." Orlando, FL. November 14, 2019.
- Sanofi Genzyme Key Opinion Leader Expert Seminar: "Future treatment options for advanced prostate cancer." Webex. November 21, 2019.
- Bayer Oncology Advisory Board: "Cognitive impairment: Impact in prostate cancer." San Diego, CA. November 23, 2019.
- Bayer Oncology Advisory Board: "Non-metastatic castration-resistant prostate cancer: Definitions and deciding to treat." San Diego, CA. November 23, 2019.
- **American Urological Association / Society of Urologic Oncology 2019 Evolving Role of the Urologist in Metastatic and Castration Resistant Prostate Cancer: A Guidelines and Case-Based Discussion: "Role of chemotherapy, treatment sequencing and future approaches." Washington, DC. December 3, 2019.**
- Merck Pharmaceuticals – Prostate Scientific Input Engagement: "KEYNOTE-365 Cohort A, B, C ASCO GU 2019 – 1st data release." San Francisco, CA. February 12, 2020.
- Peerview Live CME – Mapping the Pathways to Better Patient Outcomes in Prostate Cancer: Personal Insights and Guidance from the Patient Casebook: "Emerging novel strategies in metastatic prostate cancer." San Francisco, CA. February 14, 2020.
- Institute of Molecular Medicine and Biomedical Research – Optimal Treatment of Prostate Cancer (converted to Virtual Meeting): "Treatment of metastatic castration-resistant prostate cancer." Athens, Greece. March 13, 2020.
- Institute of Molecular Medicine and Biomedical Research – Optimal Treatment of Urothelial Cancer (converted to Virtual Meeting): "Treatment of locally advanced unresectable and metastatic disease." Athens, Greece. March 13, 2020.
- Prostate Cancer Research Institute (PCRI) 2020 Prostate Cancer Patient Conference – Mid Year Update (converted to Virtual Meeting): "Updates in advanced prostate cancer." Los Angeles, CA. March 28, 2020.
- Targeted Oncology: "Case based peer perspectives in prostate cancer." Virtual Meeting. May 7, 2020.
- Peerview Live CME: "How I think, How I treat – Learning to navigate the modern prostate cancer landscape." Virtual Meeting. June 9, 2020.
- Medscape Oncology CME: "Managing a patient with BCG-Unresponsive non-muscle-invasive bladder cancer." Virtual Meeting. June 10, 2020.
- West Coast Bayer Community Advisory Board: "Understanding the perceptions and practices shaping community oncologists' use of radium-223 dichloride." Virtual Meeting. June 18, 2020.

- Advanced Accelerator Applications Advanced Prostate Cancer Virtual Advisory Board: "Harnessing phenotypes in precision medicine and advanced prostate cancer." Virtual Meeting. June 19, 2020.
- Advanced Accelerator Applications Advanced Prostate Cancer Virtual Advisory Board: "Overview of targeted radioligand therapy and ^{177}Lu-PSMA-617 clinical trials." Virtual Meeting. June 19, 2020.
- **Section of Hematology/Oncology Special Seminar: "The future of advanced prostate cancer – curing patients with genotypic and phenotypic precision." University of Chicago by Virtual Meeting. July 17, 2020.**
- 2020 UroGPO Virtual Uro-Onc Symposium – Implications for Independent Urologists: "2020 Prostate cancer updates." Virtual Meeting. July 24, 2020.
- American Urological Association Summer Course Webinar Series - What's new in the management of hormone naïve and castrate resistant prostate cancer: "Metastatic castration-resistant prostate cancer." Virtual Meeting. August 25, 2020.
- Curio Science – Opinions in Prostate Cancer: "Metastatic castration-sensitive prostate cancer: Current treatment landscape and use of PARP inhibitors." Virtual Meeting. August 25, 2020.
- Prostate Cancer Academy: "The evolving role of novel hormonal therapy agents in advanced prostate cancer." Atlanta, GA by Virtual Meeting. October 3, 2020.
- Prostate Cancer Academy: "Optimizing the use of chemotherapy and introducing radiopharmaceuticals into our treatment paradigm for advanced prostate cancer." Atlanta, GA by Virtual Meeting. October 3, 2020.
- Curio Science – Opinions in Prostate Cancer: "Metastatic castration-sensitive prostate cancer: Current treatment landscape and use of PARP inhibitors." Dallas, TX by Virtual Meeting. October 27, 2020.
- Bayer Advisory Board: "Current approaches to managing metastatic castration-sensitive prostate cancer." Virtual Meeting. October 29, 2020.
- GU Connect Prostate Cancer Virtual MasterClass: "Non metastatic castration resistant prostate cancer." Plenary session, Virtual Meeting. November 7, 2020.
- GU Connect Prostate Cancer Virtual MasterClass: "A case-based journey through the treatment of castration-sensitive and castration-resistant prostate cancer." Virtual Meeting. November 7, 2020.
- GU Connect Prostate Cancer Virtual MasterClass: "Delivering integrated care with a multidisciplinary team – from theory to reality and the future vision." Virtual Meeting. November 7, 2020.
- Exelixis Prostate Cancer Virtual Advisory Board: "Prostate cancer current and evolving treatment landscape and practice patterns." Virtual Meeting. December 1, 2020.
- **21st Annual Meeting of the Society of Urologic Oncology: "Evaluating novel therapies and strategies – A look at the changing treatment landscape for metastatic castration-resistant prostate cancer an implications for patient care." Dallas, TX by Virtual Meeting. December 4, 2020**
- Curio Science – Opinions in Bladder Cancer: "Treatment of metastatic urothelial cancer in the post-platinum, post-immunotherapy setting." Atlanta, GA by Virtual Meeting. December 8, 2020.
- Taiwan Urological Association: "Positioning radium-223 in the metastatic castration-resistant prostate cancer treatment paradigm." Taipei, Taiwan. December 22, 2020.
- 2021 UroGPO Virtual Uro-Onc Symposium – Implications for Independent Urologists: "2021 Prostate cancer updates." Virtual Meeting. March 25, 2021.
- Targeted Oncology and HRA: "Case-based perspectives on prostate cancer." Portland, OR. March 25, 2021.

- Rocky Mountain Urological Society – Peerview Live CME: "Understanding the evolving treatment landscape in prostate cancer – How to leverage the latest advances and strategies." Denver, CO. April 9, 2021.
- IntrinsiQ – Emerging Perspectives in Prostate Cancer Focus Group: "M0 castration-resistant prostate cancer." Virtual Meeting. April 10, 2021.
- Mid Atlantic American Urological Association Mondays – Peerview Live CME: "Understanding the evolving treatment landscape in prostate cancer – How to leverage the latest advances and strategies." Virtual Meeting. April 12, 2021.
- Curio Science Community Opinions – Opinions in Bladder Cancer, An Interactive Local Workshop: "Post platinum or post immunotherapy treatment for locally advanced/metastatic urothelial carcinoma." Virtual Meeting for San Francisco, Los Angeles, and Palm Desert, CA. April 22, 2021.
- Curio Science Community Opinions – Opinions in Bladder Cancer, An Interactive Local Workshop: "Subsequent therapy for locally advanced/metastatic urothelial carcinoma." Virtual Meeting for San Francisco, Los Angeles, and Palm Desert, CA. April 22, 2021.
- Targeted Oncology and HRA: "Case-based round table meeting on prostate cancer." Virtual Meeting, Northwest United States. April 29, 2021.
- IntrinsiQ – Emerging Perspectives in Prostate Cancer Focus Group: "M0 castration-resistant prostate cancer." Virtual Meeting. May 1, 2021.
- Curio Science Community Opinions – Opinions in Bladder Cancer, An Interactive Local Workshop: "Subsequent therapy for locally advanced/metastatic urothelial carcinoma." Virtual Meeting for Kentucky and Tennessee. May 25, 2021.
- **Education Session Genitourinary Cancer – Kidney and Bladder: "Optimizing Urothelial Cancer Management From Organ-Confined to Metastastic Disease." 2021 American Society of Clinical Oncology Annual Virtual Meeting. Chicago, IL. June 4, 2021.**
- **Translational Medicine Speaker Series – Montana WWAMI Program: "Forward and reverse translation in oncology: Lessons learned from a career in prostate cancer." Montana State University, Bozeman, MT. June 11, 2021.**
- Merck Global Prostate Cancer Post-ASCO Expert Input Forum: "ASCO and GU ASCO 2021 key updates – PSMA theranostics." Virtual Meeting. June 24, 2021.
- Amgen Incorporated Monthly Grand Rounds: "That's hot! Inflaming prostate cancer." Virtual Grand Rounds Meeting. June 24, 2021.
- Genitourinary Cancer Virtual Symposium – Urothelial cancer: "Real world clinical outcomes of FGFR targeted treatment in metastatic urothelial carcinoma." Taiwan Urological Association, Virtual Meeting, Taiwan. July 24, 2021.
- Advanced Accelerator Applications: "Precision medicine in advanced prostate cancer: A phenotypic approach." Advanced Prostate Cancer Virtual Advisory Board. August 13, 2021.
- Curio Science Community Opinions – Opinions in Bladder Cancer, An Interactive Local Workshop: "Post platinum or post immunotherapy treatment for locally advanced/metastatic urothelial carcinoma." Virtual Meeting for Iowa and Minnesota. September 7, 2021.
- **American Urological Association 2021 - What's new in the management of hormone naïve and castrate resistant prostate cancer: "Metastatic castration-resistant prostate cancer." Virtual Meeting. September 12, 2021.**
- **American Urological Association 2021 – Live from AUA 2021: "Highlights in advanced prostate cancer." Virtual Meeting. September 12, 2021.**
- Bayer United States Medical Affairs Prostate Cancer Virtual Advisory Board: "Optimizing prostate cancer diagnostics – biomarker testing." Virtual Meeting. September 28, 2021.

- Onclive Institutional Perspectives in Cancer: Renal Cell Carcinoma and Bladder Cancer: "Second and later-line treatment of metastatic urothelial carcinoma." Virtual Meeting. September 30, 2021.
- Curio Science Community Opinions – Opinions in Bladder Cancer, An Interactive Local Workshop: "Post platinum or post immunotherapy treatment and adverse events for locally advanced/metastatic urothelial carcinoma." Virtual Meeting for Denver, CO. October 5, 2021.
- Curio Science Community Opinions – Opinions in Bladder Cancer, An Interactive Local Workshop: "Post platinum or post immunotherapy treatment, subsequent therapy, and adverse events for locally advanced/metastatic urothelial carcinoma." Virtual Meeting for, California. October 27, 2021.
- Curio Science Community Opinions – Opinions in Bladder Cancer, An Interactive Local Workshop: "Post platinum or post immunotherapy treatment, subsequent therapy, and adverse events for locally advanced/metastatic urothelial carcinoma." Virtual Meeting for, Portland, OR. November 18, 2021.
- 29th Annual Perspectives in Urology - Point Counterpoint: "PSMA Theranostics – ^{177}Lu-PSMA-617 recent data and considerations." Coronado Island, San Diego, CA. November 20, 2021.
- 25th Annual Southwest Prostate Cancer Symposium: "Immunotherapy in metastatic prostate cancer." Scottsdale, AZ. December 11, 2021.
- Oncternal Therapeutics R&D Day: "Metastatic castration-resistant prostate cancer: Present and Future." Virtual Meeting to San Diego, CA. January 25, 2022.
- **2022 Genitourinary Cancers Symposium: Primary Track – Urothelial Carcinoma: "Demystifying next-generation sequencing in urothelial carcinoma: A case-based approach." San Francisco, CA. February 18, 2022.**
- Bayer ARASENS Data Advisory Board: "Current approaches to managing metastatic hormone-sensitive prostate cancer and ARASENS data and planning." Seattle, WA. March 12, 2022.
- Curio Science Community Opinions – Opinions in Bladder Cancer, An Interactive Local Workshop: "Post platinum or post immunotherapy treatment, subsequent therapy, and adverse events for locally advanced/metastatic urothelial carcinoma." Virtual Meeting for Pacific Northwest. March 17, 2022.
- SWOG Spring GU Committee Meeting: "SWOG 2210: Targeted neoadjuvant treatment for patients with localized prostate cancer and germline DNA repair deficiency." Seattle, WA. April 9, 2022.
- Curio Science Community Opinions – Opinions in Bladder Cancer, An Interactive Local Workshop: "Adjuvant, front-line, post platinum or post immunotherapy, and subsequent therapy for locally advanced/metastatic urothelial carcinoma." Virtual Meeting for Portland, OR. May 26, 2022.
- Prostate Cancer Academy: "ASCO-GU/AUA/ASCO: Advanced prostate cancer highlights." Chicago, IL. June 17, 2022.
- Prostate Cancer Academy: "Metastatic hormone sensitive prostate cancer: Is monotherapy still an option? – Case studies." Chicago, IL. June 17, 2022.
- Prostate Cancer Academy: "Beyond first-line novel hormonal therapy: considerations for optimizing treatment sequence." Chicago, IL. June 17, 2022.
- ASCO Direct Highlights: 2022 Official Annual Meeting Review: "Prostate cancer." Seattle, WA. June 18, 2022.
- IntrinsiQ – Virtual Emerging Perspectives in Metastatic Hormone Sensitive Prostate Cancer Focus Group: "Metastatic hormone sensitive prostate cancer." Virtual Meeting. June 25, 2022.
- ASCO Direct Highlights: 2022 Official Annual Meeting Review: "Prostate cancer." Las Vegas, NV. July 17, 2022.

- Curio Science Community Opinions – Opinions in Bladder Cancer, An Interactive Local Workshop: "Post-platinum or post immunotherapy, and subsequent therapy for locally advanced/metastatic urothelial carcinoma." San Francisco, CA. July 20, 2022.
- Curio Science Community Opinions – Opinions in Bladder Cancer, An Interactive Local Workshop: "Post-platinum or post immunotherapy, and subsequent therapy for locally advanced/metastatic urothelial carcinoma." Las Vegas, NV. July 28, 2022.
- Curio Science Community Opinions – Opinions in Bladder Cancer, An Interactive Local Workshop: "Adjuvant therapy for muscle-invasive urothelial cancer and front-line therapy for locally advanced/metastatic urothelial carcinoma." San Diego, CA. August 11, 2022.
- IntrinsiQ – Virtual Emerging Perspectives in Metastatic Hormone Sensitive Prostate Cancer Focus Group: "Metastatic hormone sensitive prostate cancer." Virtual Meeting. September 17, 2022.
- Targeted Oncology and HRA - Case-Based Round Table Meetings: "Later line therapy for metastastic castration-resistant prostate cancer." Virtual Meeting for Arizona. September 19, 2022.
- IntrinsiQ – Virtual Challenging Cases: "Treatment of metastatic urothelial carcinoma." Virtual Meeting. September 17, 2022.
- Florida Cancer Specialists Retreat with Dr. Neil Love: "Oprimal integration of antibody drug conjugates and targeted treatment in metastatic urothelial bladder cancer." Orlando, FL. October 22, 2022.
- Merck, Sharpe, and Dohme Advisory Meeting: "Neuroendocrine determination in prostate cancer." Virtual meeting. November 14, 2022.
- Curio Science Community Opinions – Opinions in Bladder Cancer, An Interactive Local Workshop: "Post-platinum or post immunotherapy, and subsequent therapy for locally advanced/metastatic urothelial carcinoma." San Antonio, TX. November 17, 2022.
- Targeted Oncology and HRA - Case-Based Round Table Meetings: "Therapeutic sequencing for metastastic castration-resistant prostate cancer." Virtual Meeting for California, Oregon & Washington. November 22, 2022.
- IntrinsiQ – Virtual Challenging Cases: "Treatment of metastatic urothelial carcinoma." Virtual Meeting. December 13, 2022.

August 23, 2022

Michael Schweizer, MD

1. Personal Data:

2. Education:

2004 – 2008	*Temple University School of Medicine*, Philadelphia, PA Doctor of Medicine, May 2008
1999 – 2004	*University of Delaware*, Newark, DE Bachelor of Chemical Engineering, May 2004

3. Postgraduate Training:

2011 – 2014	Medical Oncology Fellowship, *The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University*, Baltimore, MD
2008 – 2011	Internal Medicine Residency, *The University of Chicago*, Chicago, IL

4. Faculty Positions Held:

2014 – Present	Assistant Professor Internal Medicine, Division of Medical Oncology, *The University of Washington*, Seattle, WA
2014 – 2019	Assistant Professor, Clinical Research Division, *Fred Hutchinson Cancer Center*, Seattle, WA
2019 – Present	Associate Professor, Clinical Research Division, *Fred Hutchinson Cancer Center*, Seattle, WA
2020 – Present	Associate Professor Internal Medicine, Division of Medical Oncology, *The University of Washington*, Seattle, WA

5. Hospital Positions Held:

2014 – Present	Attending Physician, *University of Washington Medical Center*, Seattle, WA
2014 – Present	Attending Physician, *Fred Hutchinson Cancer Center*, Seattle, WA

6. Honors:

2015	Department of Defense Physician Research Training Award
2015	Prostate Cancer Foundation Young Investigator Award
2014 – 2020	NIH Loan Repayment Program Award Recipient
2013-2014	Chief Fellow, Medical Oncology, Johns Hopkins University
Inducted 2008	Alpha Omega Alpha Medical Honor Society
Inducted 2003	OXE Chemical Engineering Honor Society
1999 – 2004	The University of Delaware Dean's List

7. Board Certification:

2013 – 2023	Medical Oncology Board Certification
2011 – 2021	Internal Medicine Board Certification

8. Current License(s) to Practice:

2014 – present	Washington State Medical License: MD60473280

9. Professional Organizations:

2012 – present	American Society of Clinical Oncology, Member ID: 166489
2012 – 2013	American Association for Cancer Research, Member ID: 274966
2014 – Present	Southwest Oncology Group, Genitourinary Oncology Committee

10. Teaching Responsibilities:

2015 – present	Precept oncology fellows in clinic approximately one ½ day per week and attend on the inpatient oncology teaching service
2015 – present	Lecture every 6-12 months at the Prostate Cancer SPORE Lecture Series
2016 – 2021	Mentor to Laura Graham MD, Currently faculty in the Division of Oncology at the University of Colorado
2016 – 2019	Small group leader, UW School of Medicine: Blood and Cancer Course
2016 – present	MED 505: First year medical student preceptorship elective (2-4 students per year)
2016 – 2020	Precept urology residents in clinic approximately one ½ day per month
2016 – present	Lecture every 12 months at Department of Medicine Core Teaching Conference Series
2016 – present	Lecture every 12 months at Fellow's Lecture Series

11. Editorial Responsibilities:

2014 – Present	Editorial Board: *Medical Oncology*
2020 – Present	Associate Editor: *Frontiers in Oncology*
2022 – Present	Editorial Board: *The Prostate*

12. Special National Responsibilities:

2014 – 2018, 2020	Grant and Funding Organization Reviews: Department of Defense Prostate Cancer Research Program

13. Special Local Responsibilities: University and hospital committees.

2015 – 2019	SPORE Pilot Grant Review
2017 – present	Member, UW/FHCRC Cancer Consortium Scientific Review Committee

2017 – present	Leader, Fred Hutchinson Cancer Center, Prostate Cancer Clinical Pathway Team
2017 – 2022	Member, Scientific Review Committee, Fred Hutch / University of Washington Cancer Consortium
2022 – present	Chair, Scientific Review Committee, Fred Hutch / University of Washington Cancer Consortium
2022 – present	Clinical Research Director, Genitourinary Oncology, Fred Hutch / University of Washington Cancer Consortium

14. Research Support

Ongoing Research Support:

Industry Sponsored Trial Schweizer (PI) 10/14/16 – 06/30/22
Protocol WO29636: A Phase III, Open-Label, Multicenter, Randomized Study of Atezolizumab vs. Observation as Adjuvant Therapy in Patients with High-Risk Muscle-Invasive Urothelial Carcinoma after Surgical Resection
The major goal of this trial is to evaluate the efficacy and safety of adjuvant treatment with atezolizumab compared with observation in patients with muscle-invasive urothelial carcinoma who are at high risk for recurrence following resection.
Role: Site PI

Industry Sponsored Trial Schweizer (PI) 07/27/18 – 04/30/23
A Phase 1b Safety and Tolerability Study of ZEN003694 in Combination with Enzalutamide or Abiraterone in Patients with Metastatic Castration-Resistant Prostate Cancer
The major goal of this study is to determine the safety, tolerability, and maximum tolerated dose of ZEN003694 in combination with enzalutamide in patients with mCRPC who have progressed during prior treatment with enzalutamide or apalutamide or with abiraterone.
criteria 2007
Role: Site PI

Investigator Initiated Trial Schweizer (PI) 08/01/18 – 03/31/23
Bipolar Androgen Therapy Plus Olaparib in Patient with Castration-Resistant Prostate Cancer
The major goal of this study is to determine whether treating prostate cancer patients with bipolar androgen therapy plus olaparib will result in high response rates, particularly in patients with DNA damage repair deficiencies.
Role: PI

Industry Sponsored Trial (Schweizer PI) 03/19/19 – 05/01/24
A Phase 1, First-in-Human, Dose Escalation Study of JNJ-63898081, in Subjects with Advanced Stage Solid Tumors
The major goal of this study is to determine whether JNJ-63898081 will direct the body's immune cells to kill the malignant cells overexpressing prostate-specific membrane antigen (PSMA).
Role: Site PI

Investigator Initiated Trial (Schweizer PI) 07/25/19 – 06/30/24
Erdafitinib plus Abiraterone Acetate or Enzalutamide in Double Negative Prostate Cancer
The major goal of this study is to determine the objective tumor response rate in subjects with measurable lesions as defined by RECIST v1.1 criteria in mCRPC patients with a DNPC molecular phenotype receiving either enzalutamide or abiraterone acetate in combination with erdafitinib.
Role: PI

Industry Sponsored Trial (Schweizer PI) 01/09/20 – 01/31/25
A Phase 3 Randomized, Double-Blind Study of Nivolumab or Placebo in Combination with Docetaxel, in Men with Metastatic Castration-resistant Prostate Cancer (CheckMate 7DX: CHECKpoint pathway and nivoluMAB clinical Trial Evaluation 7DX) (CA2097DX)
The current study aims to demonstrate that treatment with docetaxel in combination with nivolumab will be efficacious in participants with mCRPC. Additional objectives of the study include characterization of safety and tolerability, as well as pharmacokinetics, potential predictive biomarkers, and changes in patient reported outcomes for quality of life assessments.
Role: Site PI

Industry Sponsored Trial (Schweizer PI) 02/28/20 – 01/31/25
CART-PSMA-TGFβRDN-02: A Phase 1 Open-Label, Multi-Center Study of PSMA Targeted Genetically Modified Chimeric Antigen Receptor T Cells in Patients with Metastatic Castration Resistant Prostate Cancer
The major goal of this trial is to establish the safety of PSMA targeted CAR T-cell therapy in men with metastatic castration-resistant prostate cancer. This study also seeks to determine if there is preliminary evidence for clinical efficacy and explore potential biomarkers associated with response/resistance.
Role: Site PI

Industry Sponsored Trial (Schweizer PI) 03/23/20 – 02/28/25
A Phase 3, Randomized, Double-blind Trial of Pembrolizumab (MK-3475) Plus Enzalutamide Plus ADT Versus Placebo Plus Enzalutamide Plus ADT in Participants With Metastatic Hormone-Sensitive Prostate Cancer (mHSPC) (KEYNOTE-991)
The major goal is to look at Pembrolizumab (MK-3475) Plus Enzalutamide Plus ADT Versus Placebo Plus Enzalutamide Plus ADT in Participants With Metastatic Hormone-Sensitive Prostate Cancer.
Role: Site PI

Investigator Initiated Trial (Schweizer PI) 05/15/20 – 02/28/25
Durvalumab (MEDI4736) and Olaparib (AZD2281) for treatment of biochemically recurrent prostate cancer in men predicted to have a high neoantigen load: a pilot study
The major goal of this study is to evaluate the efficacy of durvalumab plus olaparib in genomic subgroups of prostate cancer expected to be sensitive to immunotherapy.
Role: PI

Industry Sponsored Trial (Schweizer PI) 08/10/20 – 08/31/25
A Phase 1 Study Exploring the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of INCB099280 in Participants With Select Advanced Solid Tumors
Major Goals: To determine the safety, tolerability of INCBO99280 (oral PDL1 inhibitor).
Role: Site PI

Industry Sponsored Trial (Schweizer PI) 01/25/21 – 02/11/26
PSMAfore: A phase III, Open-label, Multi-Center, Randomized Study Comparing 177Lu-PSMA-617 vs. a Change of androgen receptor-directed therapy in the Treatment of Taxane Naïve Men with Progressive Metastatic Castrate Resistant Prostate Cancer
Major Goals: To evaluate whether treatment with 177Lu-PSMA-617 improves the time to radiographic progression by PCWG3-modified RECIST v1.1 or death in participants with progressive PSMA-positive mCRPC compared to participants treated with androgen receptor-directed therapy.
Role: Site PI

Investigator Initiated Trial (Schweizer PI) 03/05/21 – 4/30/25
ATTAMAGE-A1.1: Phase I/II study of Autologous CD8+ and CD4+ Transgenic T cells expressing

high affinity MAGE-A1-specific T-Cell Receptor (TCR) combined with Atezolizumab in patients with metastatic MAGE-A1 expressing cancer
Major Goals: To evaluate the safety and tolerability of FH-MagIC TCR-R and to assess preliminary clinical activity
Role: PI

Industry Sponsored Trial (Schweizer PI) 07/28/21 – 08/31/26
A Phase 2 Multiple-Dose, Multiple-Arm, Parallel Assignment Study to Evaluate the Safety, Tolerability, and Preliminary Efficacy of XmAb20717 Alone or in Combination with Chemotherapy or Targeted Therapies in Selected Subjects with Metastatic Castration-Resistant Prostate Cancer
Major Goals: The major goal of this study is to determine the safety and tolerability of XmAb20717 (dual CTLA4/PD1 bispecific antibody) as monotherapy and in combination for subjects with metastatic castration-resistant prostate cancer (mCRPC) who have progressed after treatment with at least 2 prior lines of therapy
Role: Site PI

Industry Sponsored Trial (Schweizer PI) 10/13/21 – 08/31/26
Randomized Phase 2b Study of ZEN003694 in Combination with Enzalutamide versus Enzalutamide Monotherapy in Patients with Metastatic Castration-Resistant Prostate Cancer
Major Goals: To assess the effect of ZEN003694 in combination with enzalutamide versus single agent enzalutamide on radiographic progression-free survival (rPFS) in patients with metastatic castration-resistant prostate cancer (mCPRC)
Role: Site PI

Investigator Initiated Trial (Schweizer PI) 8/17/21 – 4/30/26
Olaparib in Prostate Cancer Patients With Evidence of Homologous Recombination Deficiency As Assessed Using an Integrated Genomic Signature
Major Goals: Determine the percent of patients achieving a ≥50% reduction in PSA (PSA50 response) following at least 12 weeks of treatment with olaparib 300mg twice daily in men with metastatic castration-resistant prostate cancer (mCRPC) who are iHRD+ and who have progressed on a second-generation hormonal agent (e.g. abiraterone or enzalutamide).
Role: PI

Recently Completed Research:

W81XWH-16-1-0484 Schweizer (PI) 09/30/16 – 09/29/21
Pharmacologic Dose Testosterone to Treat Castration-Resistant Prostate Cancer: Mechanisms of Action and Drivers of Response
The major goal of this project is to determining germ-line and somatic features that are predictive of response to Supra-Physiological Testosterone (SPT) and evaluate the mechanisms of action underlying the observed clinical effects of SPT.
Role: PI

Investigator Initiated Trial Schweizer (PI) 04/12/17 – 04/30/21
A Phase 2 Study of ARN-509 in Active Surveillance Patients
The major goal of this study is to determine if a 90-day course of ARN-509 will lead to a negative repeat prostate biopsy in active surveillance patients.
Role: PI

Investigator Initiated Trial McNeel (PI) 01/30/17 – 01/29/21
A Phase I Study of a DNA Vaccine Encoding Androgen Receptor Ligand-Binding Domain (AR LBD), With or Without Granulocyte Macrophage Colony-Stimulating Factor Adjuvant, in Patients With Metastatic Prostate Cancer

The major goal of this study is to determine if a vaccine called pTVG-AR can enhance patients' immune response against prostate cancer.
Role: Site PI

W81XWH-14-2-0189 Denmeade (PI) 01/01/15 – 03/29/20
A Randomized Phase II Study Comparing Bipolar Androgen Therapy vs. Enzalutamide in Asymptomatic Men with Castration Resistant Metastatic Prostate Cancer: The TRANSFORMER Trial
The major goal of this study is to determine if treatment with supraphysiologic testosterone will improve radiographic progression free survival compared to enzalutamide in men with metastatic castrate-resistant prostate cancer post-treatment with abiraterone.
Role: Site PI

15. Bibliography:

Manuscripts in referred journals:

1. Cheng, H.H., Sokolova, A.O., Gulati, R., Bowen, D., Knerr, S.A., Klemfuss, N., Grivas, P., Hsieh, A., Lee, J.K., **Schweizer, M.T.**, Yezefski, T., Zhou, A., Yu, E.Y., Nelson, P.S. & Montgomery, B. Internet-Based Germline Genetic Testing for Men With Metastatic Prostate Cancer. JCO Precis Oncol 7, e2200104 (2023). [original work]

2. **Schweizer, M.T.**, True, L., Gulati, R., Zhao, Y., Ellis, W., Schade, G., Montgomery, B., Goyal, S., Nega, K., Hakansson, A.K., Liu, Y., Davicioni, E., Pienta, K., Nelson, P.S., Lin, D. & Wright, J. Reply by Authors. J Urol 209, 362-363 (2023). [author reply]

3. **Schweizer, M.T.**, True, L., Gulati, R., Zhao, Y., Ellis, W., Schade, G., Montgomery, B., Goyal, S., Nega, K., Hakansson, A.K., Liu, Y., Davicioni, E., Pienta, K., Nelson, P.S., Lin, D. & Wright, J. Pathological Effects of Apalutamide in Lower-risk Prostate Cancer: Results From a Phase II Clinical Trial. J Urol 209, 354-363 (2023). [original work]

4. **Schweizer, M.T.**, Gulati, R., Yezefski, T., Cheng, H.H., Mostaghel, E., Haffner, M.C., Patel, R.A., De Sarkar, N., Ha, G., Dumpit, R., Woo, B., Lin, A., Panlasigui, P., McDonald, N., Lai, M., Nega, K., Hammond, J., Grivas, P., Hsieh, A., Montgomery, B., Nelson, P.S. & Yu, E.Y. Bipolar androgen therapy plus olaparib in men with metastatic castration-resistant prostate cancer. Prostate cancer and prostatic diseases (2022). [original work]

5. De Sarkar, N., Patton, R.D., Doebley, A.L., Hanratty, B., Adil, M., Kreitzman, A.J., Sarthy, J.F., Ko, M., Brahma, S., Meers, M.P., Janssens, D.H., Ang, L.S., Coleman, I.M., Bose, A., Dumpit, R.F., Lucas, J.M., Nunez, T.A., Nguyen, H.M., McClure, H.M., Pritchard, C.C., **Schweizer, M.T.**, Morrissey, C., Choudhury, A.D., Baca, S.C., Berchuck, J.E., Freedman, M.L., Ahmad, K., Haffner, M.C., Montgomery, R.B., Corey, E., Henikoff, S., Nelson, P.S. & Ha, G. Nucleosome patterns in circulating tumor DNA reveal transcriptional regulation of advanced prostate cancer phenotypes. Cancer discovery (2022). [original work]

6. Bakouny, Z., Labaki, C., Grover, P., Awosika, J., Gulati, S., Hsu, C.Y., et al., Thompson, M.A., Shah, D.P., Warner, J.L., Shyr, Y., Choueiri, T.K. & Wise-Draper, T.M. Interplay of Immunosuppression and Immunotherapy Among Patients With Cancer and COVID-19. JAMA oncology (2022). [original work]

7. Phuong, A., Marquardt, J.P., O'Malley, R., Holt, S.K., Laidlaw, G., Eagle, Z., Ngo, S., Orcutt, D., Schade, G.R., Lin, D.W., **Schweizer, M.T.**, Yezefski, T., Yu, E.Y., Montgomery, B., Grivas, P., Fintelmann, F.J. & Psutka, S.P. Changes in skeletal muscle and adipose tissue during cytotoxic chemotherapy for testicular germ cell carcinoma and associations with adverse events. Urologic oncology 40, 456.e419-456.e430 (2022). [original work]

8. Sonpavde, G.P., Maughan, B.L., McGregor, B.A., Wei, X.X., Kilbridge, K.L., Lee, R.J., Yu, E.Y., **Schweizer, M.T.**, Montgomery, R.B., Cheng, H.H., Hsieh, A.C., Jain, R., Grewal, J.S., Pico-Navarro, C., Gafoor, Z., Perschy, T. & Grivas, P. Phase II trial of CV301 vaccine combined with atezolizumab in advanced urothelial carcinoma. Cancer immunology, immunotherapy : CII (2022). [original work]

9. Symonds, L., Konnick, E., Vakar-Lopez, F., Cheng, H.H., **Schweizer, M.T.**, Nelson, P.S., Pritchard, C.C. & Montgomery, B. BRCA2 Alterations in Neuroendocrine/Small-Cell Carcinoma Prostate Cancer: A Case Series. JCO Precis Oncol 6, e2200091 (2022). [original work]

10. Fu, J., Reid, S.A., French, B., Hennessy, C., Hwang, C., Gatson, N.T., Duma, N., Mishra, S., Nguyen, R., Hawley, J.E., Singh, S.R.K., Chism, D.D., Venepalli, N.K., Warner, J.L., Choueiri, T.K., Schmidt, A.L., Fecher, L.A., Girard, J.E., Bilen, M.A., Ravindranathan, D., Goyal, S., Wise-Draper, T.M., Park, C., Painter, C.A., McGlown, S.M., de Lima Lopes, G., Jr., Serrano, O.K. & Shah, D.P. Racial Disparities in COVID-19 Outcomes Among Black and White Patients With Cancer. JAMA Netw Open 5, e224304 (2022). [original work]

11. Graham, L.S. & **Schweizer, M.T.** Mismatch repair deficiency and clinical implications in prostate cancer. The Prostate 82 Suppl 1, S37-s44 (2022). [review]

12. Hawley, J.E., Sun, T., Chism, D.D., Duma, N., Fu, J.C., Gatson, N.T.N., Mishra, S., Nguyen, R.H., Reid, S.A., Serrano, O.K., Singh, S.R.K., Venepalli, N.K., Bakouny, Z., Bashir, B., Bilen, M.A., Caimi, P.F., Choueiri, T.K., Dawsey, S.J., Fecher, L.A., Flora, D.B., Friese, C.R., Glover, M.J., Gonzalez, C.J., Goyal, S., Halfdanarson, T.R., Hershman, D.L., Khan, H., Labaki, C., Lewis, M.A., McKay, R.R., Messing, I., Pennell, N.A., Puc, M., Ravindranathan, D., Rhodes, T.D., Rivera, A.V., Roller, J., Schwartz, G.K., Shah, S.A., Shaya, J.A., Streckfuss, M., Thompson, M.A., Wulff-Burchfield, E.M., Xie, Z., Yu, P.P., Warner, J.L., Shah, D.P., French, B. & Hwang, C. Assessment of Regional Variability in COVID-19 Outcomes Among Patients With Cancer in the United States. JAMA Netw Open 5, e2142046 (2022). [original work]

13. Markowski, M.C., Wang, H., De Marzo, A.M., **Schweizer, M.T.**, Antonarakis, E.S. & Denmeade, S.R. Clinical Efficacy of Bipolar Androgen Therapy in Men with Metastatic Castration-Resistant Prostate Cancer and Combined Tumor-Suppressor Loss. Eur Urol Open Sci 41, 112-115 (2022). [original work]

14. De Sarkar, N., Dasgupta, S., Chatterjee, P., Coleman, I., Ha, G., Ang, L.S., Kohlbrenner, E.A., Frank, S.B., Nunez, T.A., Salipante, S.J., Corey, E., Morrissey, C., Van Allen, E., **Schweizer, M.T.**, Haffner, M.C., Patel, R., Hanratty, B., Lucas, J.M., Dumpit, R.F., Pritchard, C.C., Montgomery, R.B. & Nelson, P.S. Genomic attributes of homology-directed DNA repair deficiency in metastatic prostate cancer. JCI Insight 6(2021). [original work]

15. Schmidt, A.L., Tucker, M.D., Bakouny, Z., Labaki, C., Hsu, C.Y., Shyr, Y., Armstrong, A.J., Beer, T.M., Bijjula, R.R., Bilen, M.A., Connell, C.F., Dawsey, S.J., Faller, B., Gao, X., Gartrell, B.A., Gill, D., Gulati, S., Halabi, S., Hwang, C., Joshi, M., Khaki, A.R., Menon, H., Morris, M.J., Puc, M., Russell, K.B., Shah, N.J., Sharifi, N., Shaya, J., **Schweizer, M.T.**, Steinharter, J., Wulff-Burchfield, E.M., Xu, W., Zhu, J., Mishra, S., Grivas, P., Rini, B.I., Warner, J.L., Zhang, T., Choueiri, T.K., Gupta, S. & McKay, R.R. Association Between Androgen Deprivation Therapy and Mortality Among Patients With Prostate Cancer and COVID-19. JAMA Netw Open 4, e2134330 (2021). [original work]

16. Graham, L.S., Pritchard, C.C. & **Schweizer, M.T.** Hypermutation, Mismatch Repair Deficiency, and Defining Predictors of Response to Checkpoint Blockade. *Clinical cancer research : an official journal of the American Association for Cancer Research* (2021). [editorial]

17. Koshkin, V.S., Patel, V.G., Ali, A., Bilen, M.A., Ravindranathan, D., Park, J.J., Kellezi, O., Cieslik, M., Shaya, J., Cabal, A., Brown, L., Labriola, M., Graham, L.S., Pritchard, C., Tripathi, A., Nusrat, S., Barata, P., Jang, A., Chen, S.R., Garje, R., Acharya, L., Hwang, C., Pilling, A., Oh, W., Jun, T., Natesan, D., Nguyen, C., Kilari, D., Pierro, M., Thapa, B., Cackowski, F., Mack, A., Heath, E., Marshall, C.H., Tagawa, S.T., Halabi, S., **Schweizer, M.T.**, Armstrong, A., Dorff, T., Alva, A. & McKay, R. PROMISE: a real-world clinical-genomic database to address knowledge gaps in prostate cancer. *Prostate cancer and prostatic diseases* (2021). [white paper]

18. Mostaghel, E.A., Marck, B.T., Kolokythas, O., Chew, F., Yu, E.Y., **Schweizer, M.T.**, Cheng, H.H., Kantoff, P.W., Balk, S.P., Taplin, M.E., Sharifi, N., Matsumoto, A.M., Nelson, P.S. & Montgomery, R.B. Circulating and Intratumoral Adrenal Androgens Correlate with Response to Abiraterone in Men with Castration-Resistant Prostate Cancer. *Clinical cancer research : an official journal of the American Association for Cancer Research* **27**, 6001-6011 (2021). [original work]

19. **Schweizer, M.T.**, Sivakumar, S., Tukachinsky, H., Coleman, I., De Sarkar, N., Yu, E.Y., Konnick, E.Q., Nelson, P.S., Pritchard, C.C. & Montgomery, B. Concordance of DNA Repair Gene Mutations in Paired Primary Prostate Cancer Samples and Metastatic Tissue or Cell-Free DNA. *JAMA oncology* **7**, 1-5 (2021). [original work]

20. Sokolova, A.O., Marshall, C.H., Lozano, R., Gulati, R., Ledet, E.M., De Sarkar, N., Grivas, P., Higano, C.S., Montgomery, B., Nelson, P.S., Olmos, D., Sokolov, V., **Schweizer, M.T.**, Yezefski, T.A., Yu, E.Y., Paller, C.J., Sartor, O., Castro, E., Antonarakis, E.S. & Cheng, H.H. Efficacy of systemic therapies in men with metastatic castration resistant prostate cancer harboring germline ATM versus BRCA2 mutations. *The Prostate* **81**, 1382-1389 (2021). [original work]

21. Thompson, M.A., Henderson, J.P., Shah, P.K., Rubinstein, S.M., Joyner, M.J., Choueiri, T.K., Flora, D.B., Griffiths, E.A., Gulati, A.P., Hwang, C., Koshkin, V.S., Papadopoulos, E.B., Robilotti, E.V., Su, C.T., Wulff-Burchfield, E.M., Xie, Z., Yu, P.P., Mishra, S., Senefeld, J.W., Shah, D.P. & Warner, J.L. Association of Convalescent Plasma Therapy With Survival in Patients With Hematologic Cancers and COVID-19. *JAMA oncology* **7**, 1167-1175 (2021). [original work]

22. Denmeade, S.R., Wang, H., Agarwal, N., Smith, D.C., **Schweizer, M.T.**, Stein, M.N., Assikis, V., Twardowski, P.W., Flaig, T.W., Szmulewitz, R.Z., Holzbeierlein, J.M., Hauke, R.J., Sonpavde, G., Garcia, J.A., Hussain, A., Sartor, O., Mao, S., Cao, H., Fu, W., Wang, T., Abdallah, R., Lim, S.J., Bolejack, V., Paller, C.J., Carducci, M.A., Markowski, M.C., Eisenberger, M.A. & Antonarakis, E.S. TRANSFORMER: A Randomized Phase II Study Comparing Bipolar Androgen Therapy Versus Enzalutamide in Asymptomatic Men With Castration-Resistant Metastatic Prostate Cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 39, 1371-1382 (2021). [original work]

23. Diamantopoulos, L.N., Sekar, R.R., Holt, S.K., Khaki, A.R., Miller, N.J., Gadzinski, A., Nyame, Y.A., Vakar-Lopez, F., Tretiakova, M.S., Psutka, S.P., Gore, J.L., Lin, D.W., Schade, G.R., Hsieh, A.C., Lee, J.K., Yezefski, T., **Schweizer, M.T.**, Cheng, H.H., Yu, E.Y., True, L.D., Montgomery, R.B., Grivas, P. & Wright, J.L. Patterns and timing of perioperative blood transfusion and association with outcomes after radical cystectomy. Urologic oncology (2021). [original work]

24. Graham, L.S., True, L.D., Gulati, R., Schade, G.R., Wright, J., Grivas, P., Yezefski, T., Nega, K., Alexander, K., Hou, W.M., Yu, E.Y., Montgomery, B., Mostaghel, E.A., Matsumoto, A.A., Marck, B., Sharifi, N., Ellis, W.J., Reder, N.P., Lin, D.W., Nelson, P.S. & **Schweizer, M.T.**

Targeting backdoor androgen synthesis through AKR1C3 inhibition: A presurgical hormonal ablative neoadjuvant trial in high-risk localized prostate cancer. The Prostate 81, 418-426 (2021). [original work]

25. A Systematic Framework to Rapidly Obtain Data on Patients with Cancer and COVID-19: CCC19 Governance, Protocol, and Quality Assurance. Cancer Cell 38, 761-766 (2020). [original work]

26. DeLucia, D.C., Cardillo, T.M., Ang, L., Labrecque, M.P., Zhang, A., Hopkins, J.E., De Sarkar, N., Coleman, I., da Costa, R.M.G., Corey, E., True, L.D., Haffner, M.C., **Schweizer, M.T.**, Morrissey, C., Nelson, P.S. & Lee, J.K. Regulation of CEACAM5 and Therapeutic Efficacy of an Anti-CEACAM5-SN38 Antibody-drug Conjugate in Neuroendocrine Prostate Cancer. Clin Cancer Res (2020). [original work]

27. Diamantopoulos, L.N., Holt, S.K., Khaki, A.R., Sekar, R.R., Gadzinski, A., Nyame, Y.A., Vakar-Lopez, F., Tretiakova, M.S., Psutka, S.P., Gore, J.L., Lin, D.W., Schade, G.R., Hsieh, A.C., Lee, J.K., Yezefski, T., **Schweizer, M.T.**, Cheng, H.H., Yu, E.Y., True, L.D., Montgomery, R.B., Grivas, P. & Wright, J.L. Response to Neoadjuvant Chemotherapy and Survival in Micropapillary Urothelial Carcinoma: Data From a Tertiary Referral Center and the Surveillance, Epidemiology, and End Results (SEER) Program. Clin Genitourin Cancer (2020). [original work]
28. Jensen, K., Konnick, E.Q., **Schweizer, M.T.**, Sokolova, A.O., Grivas, P., Cheng, H.H., Klemfuss, N.M., Beightol, M., Yu, E.Y., Nelson, P.S., Montgomery, B. & Pritchard, C.C. Association of Clonal Hematopoiesis in DNA Repair Genes With Prostate Cancer Plasma Cell-free DNA Testing Interference. JAMA Oncol 7, 107-110 (2021). [original work]

29. Carlson, A.S., Acevedo, R.I., Lim, D.M., Gulati, R., Gawne, A., Sokolova, A.O., Cheng, H.H., Nelson, P.S., Montgomery, R.B., Yu, E.Y. & **Schweizer, M.T.** Impact of mutations in homologous recombination repair genes on treatment outcomes for metastatic castration resistant prostate cancer. *PLoS One* **15**, e0239686 (2020). [original work]

30. McKay, R.R., Hafron, J.M., Ferro, C., Wilfehrt, H.M., Fitch, K., Flanders, S.C., Fabrizio, M.D. & **Schweizer, M.T.** A Retrospective Observational Analysis of Overall Survival with Sipuleucel-T in Medicare Beneficiaries Treated for Advanced Prostate Cancer. *Adv Ther* (2020). [original work]

31. Aggarwal, R.R., **Schweizer, M.T.**, Nanus, D.M., Pantuck, A.J., Heath, E.I., Campeau, E., Attwell, S., Norek, K., Snyder, M., Bauman, L., Lakhotia, S., Feng, F.Y., Small, E.J., Abida, W. & Alumkal, J.J. A Phase Ib/IIa Study of the Pan-BET Inhibitor ZEN-3694 in Combination with Enzalutamide in Patients with Metastatic Castration-resistant Prostate Cancer. Clin Cancer Res (2020). [original work]

32. Markowski, M.C., Wang, H., Sullivan, R., Rifkind, I., Sinibaldi, V., **Schweizer, M.T.**, Teply, B.A., Ngomba, N., Fu, W., Carducci, M.A., Paller, C.J., Marshall, C.H., Eisenberger, M.A., Luo, J., Antonarakis, E.S. & Denmeade, S.R. A Multicohort Open-label Phase II Trial of Bipolar Androgen Therapy in Men with Metastatic Castration-resistant Prostate Cancer (RESTORE): A Comparison of Post-abiraterone Versus Post-enzalutamide Cohorts. Eur Urol (2020). [original work]

33. **Schweizer, M.T.**, Cheng, H.H., Nelson, P.S. & Montgomery, R.B. Two Steps Forward and One Step Back for Precision in Prostate Cancer Treatment. J Clin Oncol, Jco2001755 (2020). [editorial]

34. **Schweizer, M.T.**, Ha, G., Gulati, R., Brown, L.C., McKay, R.R., Dorff, T., Hoge, A.C.H., Reichel, J., Vats, P., Kilari, D., Patel, V., Oh, W.K., Chinnaiyan, A., Pritchard, C.C., Armstrong,

A.J., Montgomery, R.B. & Alva, A. CDK12-Mutated Prostate Cancer: Clinical Outcomes With Standard Therapies and Immune Checkpoint Blockade. JCO Precis Oncol 4, 382-392 (2020). [original work]

35. Kyriakopoulos, C.E., Eickhoff, J., Ferrari, A.C., **Schweizer, M.T.**, Wargowski, E., Olson, B.M. & McNeel, D.G. Multicenter Phase 1 Trial of a DNA Vaccine Encoding the Androgen Receptor Ligand Binding Domain (pTVG-AR, MVI-118) in Patients with Metastatic Prostate Cancer. Clinical cancer research : an official journal of the American Association for Cancer Research (2020). [original work]

36. Graham, L.S., Montgomery, B., Cheng, H.H., Yu, E.Y., Nelson, P.S., Pritchard, C., Erickson, S., Alva, A. & **Schweizer, M.T.** Mismatch repair deficiency in metastatic prostate cancer: Response to PD-1 blockade and standard therapies. PloS one 15, e0233260 (2020). [original work]

37. **Schweizer, M.T.**, Antonarakis, E.S., Bismar, T.A., Guedes, L.B., Cheng, H.H., Tretiakova, M.S., Vakar-Lopez, F., Klemfuss, N., Konnick, E.Q., Mostaghel, E.A., Hsieh, A.C., Nelson, P.S., Yu, E.Y., Montgomery, R.B., True, L.D., Epstein, J.I., Lotan, T.L. & Pritchard, C.C. Genomic Characterization of Prostatic Ductal Adenocarcinoma Identifies a High Prevalence of DNA Repair Gene Mutations. JCO Precis Oncol 3(2019). [original work]

38. **Schweizer, M.T.** & Yu, E.Y. *"Matching" the "mismatch" repair deficient prostate cancer with immunotherapy*. Clinical cancer research: an official journal of the American Association for Cancer Research (2020). [commentary]

39. Graham, L.S., Schade, G. & **Schweizer, M.T.** Multimodality Treatment of Bilateral Wilms Tumor in a Pregnant Female. Urology (2019). [case report]

40. Labrecque, M.P., Coleman, I.M., Brown, L.G., True, L.D., Kollath, L., Lakely, B., Nguyen, H.M., Yang, Y.C., Gil da Costa, R.M., Kaipainen, A., Coleman, R., Higano, C.S., Yu, E.Y., Cheng, H.H., Mostaghel, E.A., Montgomery, B., **Schweizer, M.T.**, Hsieh, A.C., Lin, D.W., Corey, E., Nelson, P.S. & Morrissey, C. Molecular profiling stratifies diverse phenotypes of treatment-refractory metastatic castration-resistant prostate cancer. The Journal of clinical investigation 130(2019). [original work]

41. *Chatterjee, P., †**Schweizer, M.T.**, Lucas, J.M., Coleman, I., Nyquist, M.D., Frank, S.B., Tharakan, R., Mostaghel, E., Luo, J., Pritchard, C.C., Lam, H.M., Corey, E., Antonarakis, E.S., Denmeade, S.R. & Nelson, P.S. Supraphysiological androgens suppress prostate cancer growth through androgen receptor-mediated DNA damage. The Journal of clinical investigation 130(2019).
†Co-first author

42. Lam, H.M., Nguyen, H.M., Labrecque, M.P., Brown, L.G., Coleman, I.M., Gulati, R., Lakely, B., Sondheim, D., Chatterjee, P., Marck, B.T., Matsumoto, A.M., Mostaghel, E.A., **Schweizer, M.T.**, Nelson, P.S. & Corey, E. Durable Response of Enzalutamide-resistant Prostate Cancer to Supraphysiological Testosterone Is Associated with a Multifaceted Growth Suppression and Impaired DNA Damage Response Transcriptomic Program in Patient-derived Xenografts. European urology (2019).

43. Winters, B.R., De Sarkar, N., Arora, S., Bolouri, H., Jana, S., Vakar-Lopez, F., Cheng, H.H., **Schweizer, M.T.**, Yu, E.Y., Grivas, P., Lee, J.K., Kollath, L., Holt, S.K., McFerrin, L., Ha, G., Nelson, P.S., Montgomery, R.B., Wright, J.L., Lam, H.M. & Hsieh, A.C. Genomic distinctions between metastatic lower and upper tract urothelial carcinoma revealed through rapid autopsy. JCI insight 5(2019).

44. **Schweizer MT**, Antonarakis ES, Bismar TA, Guedes LB, Cheng HH, Tretiakova MS, Vakar-Lopez F, Klemfuss N, Konnick EQ, Mostaghel EA, Hsieh AC, Nelson PS, Yu EY, Montgomery RB, True LD, Epstein JI, Lotan TL, Pritchard CC. Genomic characterization of prostatic ductal adenocarcinoma identifies a high prevalence of DNA repair gene mutations. JCO Precision Oncology (In Press). [original work]

45. Brennen, W.N., **Schweizer, M.T.**, Wang, H., Bivalacqua, T.J., Partin, A.W., Lim, S.J., Chapman, C., Abdallah, R., Levy, O., Bhowmick, N.A., Karp, J.M., De Marzo, A., Isaacs, J.T. & Denmeade, S.R. In Reply to the Letter to the Editor from Raj et al.: Clinical Evidence Indicates Allogeneic Mesenchymal Stem Cells Do Not Pose a Significant Risk for Cancer Progression in the Context of Cell-Based Drug Delivery. Stem cells translational medicine (2019). [response letter]

46. ***Schweizer, M.T.**, Gulati, R., Beightol, M., Konnick, E.Q., Cheng, H.H., Klemfuss, N., De Sarkar, N., Yu, E.Y., Montgomery, R.B., Nelson, P.S. & Pritchard, C.C. Clinical determinants for successful circulating tumor DNA analysis in prostate cancer. The Prostate (2019). [original work]

47. Marshall, C.H., Sokolova, A.O., McNatty, A.L., Cheng, H.H., Eisenberger, M.A., Bryce, A.H., **Schweizer, M.T.** & Antonarakis, E.S. Differential Response to Olaparib Treatment Among Men with Metastatic Castration-resistant Prostate Cancer Harboring BRCA1 or BRCA2 Versus ATM Mutations. European urology (2019). [original work]

48. ***Schweizer, M.T.**, Wang, H., Bivalacqua, T.J., Partin, A.W., Lim, S.J., Chapman, C., Abdallah, R., Levy, O., Bhowmick, N.A., Karp, J.M., De Marzo, A., Isaacs, J.T., Brennen, W.N. & Denmeade, S.R. A Phase I Study to Assess the Safety and Cancer-Homing Ability of Allogeneic Bone Marrow-Derived Mesenchymal Stem Cells in Men with Localized Prostate Cancer. Stem cells translational medicine (2019). [original work]

49. Nava Rodrigues, D., Rescigno, P., Liu, D., Yuan, W., Carreira, S., Lambros, M.B., Seed, G., Mateo, J., Riisnaes, R., Mullane, S., Margolis, C., Miao, D., Miranda, S., Dolling, D., Clarke, M., Bertan, C., Crespo, M., Boysen, G., Ferreira, A., Sharp, A., Figueiredo, I., Keliher, D., Aldubayan, S., Burke, K.P., Sumanasuriya, S., Fontes, M.S., Bianchini, D., Zafeiriou, Z., Teixeira Mendes, L.S., Mouw, K., **Schweizer, M.T.**, Pritchard, C.C., Salipante, S., Taplin, M.E., Beltran, H., Rubin, M.A., Cieslik, M., Robinson, D., Heath, E., Schultz, N., Armenia, J., Abida, W., Scher, H., Lord, C., D'Andrea, A., Sawyers, C.L., Chinnaiyan, A.M., Alimonti, A., Nelson, P.S., Drake, C.G., Van Allen, E.M. & de Bono, J.S. Immunogenomic analyses associate immunological alterations with mismatch repair defects in prostate cancer. The Journal of clinical investigation 128, 4441-4453 (2018). [original work]

50. **Schweizer, M.T.**, Haugk, K., McKiernan, J.S., Gulati, R., Cheng, H.H., Maes, J.L., Dumpit, R.F., Nelson, P.S., Montgomery, B., McCune, J.S., Plymate, S.R. & Yu, E.Y. Correction: A phase I study of niclosamide in combination with enzalutamide in men with castration-resistant prostate cancer. PloS one 13, e0202709 (2018). [corrigendum]

51. ***Schweizer, M.T.**, Haugk, K., McKiernan, J.S., Gulati, R., Cheng, H.H., Maes, J.L., Dumpit, R.F., Nelson, P.S., Montgomery, B., McCune, J.S., Plymate, S.R. & Yu, E.Y. A phase I study of niclosamide in combination with enzalutamide in men with castration-resistant prostate cancer. PloS one 13, e0198389 (2018). [original work]

52. Hempelmann, J.A., Lockwood, C.M., Konnick, E.Q., **Schweizer, M.T.**, Antonarakis, E.S., Lotan, T.L., Montgomery, B., Nelson, P.S., Klemfuss, N., Salipante, S.J. & Pritchard, C.C. Microsatellite instability in prostate cancer by PCR or next-generation sequencing. Journal for immunotherapy of cancer 6, 29 (2018). [original work]

53. Teply, B.A., Wang, H., Luber, B., Sullivan, R., Rifkind, I., Bruns, A., Spitz, A., DeCarli, M., Sinibaldi, V., Pratz, C.F., Lu, C., Silberstein, J.L., Luo, J., **Schweizer, M.T.**, Drake, C.G., Carducci, M.A., Paller, C.J., Antonarakis, E.S., Eisenberger, M.A. & Denmeade, S.R. Bipolar androgen therapy in men with metastatic castration-resistant prostate cancer after progression on enzalutamide: an open-label, phase 2, multicohort study. The Lancet. Oncology 19, 76-86 (2018). [original work]

54. Mohammad, O.S., Nyquist, M.D., **Schweizer, M.T.**, Balk, S.P., Corey, E., Plymate, S., Nelson, P.S. & Mostaghel, E.A. Supraphysiologic Testosterone Therapy in the Treatment of Prostate Cancer: Models, Mechanisms and Questions. Cancers 9(2017). [review]

55. **Schweizer, M.T.**, Hancock, M.L., Getzenberg, R.H. & Yu, E.Y. Hormone levels following surgical and medical castration: defining optimal androgen suppression. Asian journal of andrology 20, 405-406 (2018). [original work]

56. Graham, L., True, L.D. & **Schweizer, M.T.** Metastatic Adenocarcinoma of the Epididymis: A Case Report and Brief Literature Review. Clinical genitourinary cancer 16, e335-e338 (2018). [case report]

57. **Schweizer, M.T.** & Antonarakis, E.S. Prognostic and therapeutic implications of DNA repair gene mutations in advanced prostate cancer. Clinical advances in hematology & oncology : H&O 15, 785-795 (2017). [review]

58. Bluemn, E.G., Coleman, I.M., Lucas, J.M., Coleman, R.T., Hernandez-Lopez, S., Tharakan, R., Bianchi-Frias, D., Dumpit, R.F., Kaipainen, A., Corella, A.N., Yang, Y.C., Nyquist, M.D., Mostaghel, E., Hsieh, A.C., Zhang, X., Corey, E., Brown, L.G., Nguyen, H.M., Pienta, K., Ittmann, M., **Schweizer, M.**, True, L.D., Wise, D., Rennie, P.S., Vessella, R.L., Morrissey, C. & Nelson, P.S. Androgen Receptor Pathway-Independent Prostate Cancer Is Sustained through FGF Signaling. Cancer cell 32, 474-489.e476 (2017). [original work]

59. Guedes, L.B., Antonarakis, E.S., **Schweizer, M.T.**, Mirkheshti, N., Almutairi, F., Park, J.C., Glavaris, S., Hicks, J., Eisenberger, M.A., De Marzo, A.M., Epstein, J.I., Isaacs, W.B., Eshleman, J.R., Pritchard, C.C. & Lotan, T.L. MSH2 Loss in Primary Prostate Cancer. Clinical cancer research : an official journal of the American Association for Cancer Research 23, 6863-6874 (2017). [original work]

60. Chi, E.A. & **Schweizer, M.T.** Durable Response to Immune Checkpoint Blockade in a Platinum-Refractory Patient With Nonseminomatous Germ Cell Tumor. Clinical genitourinary cancer 15, e855-e857 (2017). [case report]

61. **Schweizer, M.T.**, Antonarakis, E.S. & Denmeade, S.R. Bipolar Androgen Therapy: A Paradoxical Approach for the Treatment of Castration-resistant Prostate Cancer. European urology 72, 323-325 (2017). [review]

62. **Schweizer, M.T.** & Yu, E.Y. AR-Signaling in Human Malignancies: Prostate Cancer and Beyond. Cancers 9(2017). [review]

63. **Schweizer, M.T.**, Cheng, H.H., Tretiakova, M.S., Vakar-Lopez, F., Klemfuss, N., Konnick, E.Q., Mostaghel, E.A., Nelson, P.S., Yu, E.Y., Montgomery, B., True, L.D. & Pritchard, C.C. Mismatch repair deficiency may be common in ductal adenocarcinoma of the prostate. Oncotarget 7, 82504-82510 (2016). [original work]

64. **Schweizer, M.T.** & Yu, E.Y. Targeting intratumoral androgens: statins and beyond. Therapeutic advances in medical oncology 8, 388-395 (2016). [review]

65. **Schweizer, M.T.** & Plymate, S.R. Response: letter to the editor. Expert opinion on therapeutic targets 21, 229 (2017). [response letter]

66. **Schweizer, M.T.**, Wang, H., Luber, B., Nadal, R., Spitz, A., Rosen, D.M., Cao, H., Antonarakis, E.S., Eisenberger, M.A., Carducci, M.A., Paller, C. & Denmeade, S.R. Bipolar Androgen Therapy for Men With Androgen Ablation Naive Prostate Cancer: Results From the Phase II BATMAN Study. The Prostate 76, 1218-1226 (2016). [original work]

67. Cheng, H.H., Klemfuss, N., Montgomery, B., Higano, C.S., **Schweizer, M.T.**, Mostaghel, E.A., McFerrin, L.G., Yu, E.Y., Nelson, P.S. & Pritchard, C.C. A Pilot Study of Clinical Targeted Next Generation Sequencing for Prostate Cancer: Consequences for Treatment and Genetic Counseling. The Prostate 76, 1303-1311 (2016). [original work]

68. **Schweizer, M.T.**, Gulati, R., Mostaghel, E.A., Nelson, P.S., Montgomery, R.B., Yu, E.Y. & Cheng, H.H. Docetaxel-related toxicity in metastatic hormone-sensitive and metastatic castration-resistant prostate cancer. Medical oncology (Northwood, London, England) 33, 77 (2016). [original work]

69. Graham, L. & **Schweizer, M.T.** Targeting persistent androgen receptor signaling in castration-resistant prostate cancer. Medical oncology (Northwood, London, England) 33, 44 (2016). [review]

70. **Schweizer, M.T.** & Plymate, S.R. Targeting constitutively active androgen receptor splice variants in castration resistant prostate cancer. Expert opinion on therapeutic targets 20, 903-906 (2016). [review]

71. **Schweizer, M.T.** & Yu, E.Y. Persistent androgen receptor addiction in castration-resistant prostate cancer. Journal of hematology & oncology 8, 128 (2015). [review]

72. **Schweizer, M.T.** & Antonarakis, E.S. Liquid biopsy: Clues on prostate cancer drug resistance. Science translational medicine 7, 312fs345 (2015). [review]

73. Maughan, B.L., Xhou, X.C., Suzman, D.L., Nadal, R., Bassi, S., **Schweizer, M.T.** & Antonarakis, E.S. Optimal sequencing of docetaxel and abiraterone in men with metastatic castration-resistant prostate cancer. The Prostate 75, 1814-1820 (2015). [original work]

74. ***Schweizer, M.T.**, Antonarakis, E.S., Wang, H., Ajiboye, A.S., Spitz, A., Cao, H., Luo, J., Haffner, M.C., Yegnasubramanian, S., Carducci, M.A., Eisenberger, M.A., Isaacs, J.T. & Denmeade, S.R. Effect of bipolar androgen therapy for asymptomatic men with castration-resistant prostate cancer: results from a pilot clinical study. Science translational medicine 7, 269ra262 (2015). [original work]

75. Nadal, R., Zhang, Z., Rahman, H., **Schweizer, M.T.**, Denmeade, S.R., Paller, C.J., Carducci, M.A., Eisenberger, M.A. & Antonarakis, E.S. Clinical activity of enzalutamide in Docetaxel-naive and Docetaxel-pretreated patients with metastatic castration-resistant prostate cancer. The Prostate 74, 1560-1568 (2014). [original work]

76. Suzman, D.L., Luber, B., **Schweizer, M.T.**, Nadal, R. & Antonarakis, E.S. Clinical activity of enzalutamide versus docetaxel in men with castration-resistant prostate cancer progressing after abiraterone. The Prostate 74, 1278-1285 (2014). [original work]

77. Nadal, R., **Schweizer, M.**, Kryvenko, O.N., Epstein, J.I. & Eisenberger, M.A. Small cell carcinoma of the prostate. Nature reviews. Urology 11, 213-219 (2014). [review]

78. **Schweizer, M.T.**, Zhou, X.C., Wang, H., Bassi, S., Carducci, M.A., Eisenberger, M.A. & Antonarakis, E.S. The influence of prior abiraterone treatment on the clinical activity of docetaxel in men with metastatic castration-resistant prostate cancer. European urology 66, 646-652 (2014). [original work]

79. **Schweizer, M.T.** & Drake, C.G. Immunotherapy for prostate cancer: recent developments and future challenges. Cancer metastasis reviews 33, 641-655 (2014). [review]

80. **Schweizer, M.T.** & Antonarakis, E.S. Chemotherapy and its evolving role in the management of advanced prostate cancer. Asian journal of andrology 16, 334-340 (2014). [review]

81. **Schweizer, M.T.**, Lin, J., Blackford, A., Bardia, A., King, S., Armstrong, A.J., Rudek, M.A., Yegnasubramanian, S. & Carducci, M.A. Pharmacodynamic study of disulfiram in men with non-metastatic recurrent prostate cancer. Prostate cancer and prostatic diseases 16, 357-361 (2013). [original work]

82. **Schweizer, M.T.**, Zhou, X.C., Wang, H., Yang, T., Shaukat, F., Partin, A.W., Eisenberger, M.A. & Antonarakis, E.S. Metastasis-free survival is associated with overall survival in men with PSA-recurrent prostate cancer treated with deferred androgen deprivation therapy. Annals of oncology: official journal of the European Society for Medical Oncology / ESMO 24, 2881-2886 (2013). [original work]

83. **Schweizer, M.T.**, Huang, P., Kattan, M.W., Kibel, A.S., de Wit, R., Sternberg, C.N., Epstein, J.I. & Eisenberger, M.A. Adjuvant leuprolide with or without docetaxel in patients with high-risk prostate cancer after radical prostatectomy (TAX-3501): important lessons for future trials. Cancer 119, 3610-3618 (2013). [original work]

84. **Schweizer, M.T.** & Carducci, M.A. From bevacizumab to tasquinimod: angiogenesis as a therapeutic target in prostate cancer. Cancer journal (Sudbury, Mass.) 19, 99-106 (2013). [review]

85. **Schweizer, M.T.** & Antonarakis, E.S. Abiraterone acetate: a hat trick of clinical benefits. The Lancet. Oncology 13, 1173-1174 (2012). [review]

86. **Schweizer, M.T.** & Antonarakis, E.S. Abiraterone and other novel androgen-directed strategies for the treatment of prostate cancer: a new era of hormonal therapies is born. Therapeutic advances in urology 4, 167-178 (2012). [review]

87. **Schweizer, M.T.**, Mehta, R., Salgia, R. & Villaflor, V.M. Takotsubo cardiomyopathy in a patient with squamous cell esophageal carcinoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 29, e598-600 (2011). [case report]

Book chapters.

1. **Schweizer MT**, Montgomery RB. Sequencing Therapies in Metastatic Castration Resistant Prostate Cancer. In: Balaji K, ed. Castration Resistant Prostate Cancer: Springer Science; 2015.

Published books, videos, software, etc.

N/A

Other publications (e.g., in non-refereed journals and letters to the editor).

N/A

Abstracts

1. **Schweizer, M.T.**, Penkov, K.D., Tolcher, A.W., Choudhury, A.D., Doronin, V., Aljumaily, R., Calvo, E., Frank, R.C., Hamm, J.T., Moreno Garcia, V., Vorobyev, V., Billotte, S., Bowler, T., Chen, J., Lin, T., Liu, L., Maity, A., Sharma, S. & Johnson, M.L. Phase I trial of PF-06821497, a potent and selective inhibitor of enhancer of zeste homolog 2 (EZH2), in follicular lymphoma (FL), small cell lung cancer (SCLC) and castration-resistant prostate cancer (CRPC). in *ESMO Congress*, Paris, France.

2. **Schweizer MT**, Gulati R, Yezefski T, Cheng HH, Sievers C, Dumpit R, Alexander K, McDonald N, Lai M, Nega K, Hammond J, Grivas P, Hsieh A, Montgomery B, Nelson PS, Yu EY. Bipolar Androgen Therapy (BAT) plus Olaparib in Men with Metastatic Castration-resistant Prostate Cancer (mCRPC). Poster presented at: 2021 ESMO Annual Meeting. Virtual.

3. **Schweizer MT**, True L, Ellis W, Schade G, Montgomery RB, Goyal S, Nega K, Pienta K, Nelson P, Lin D, Wright J. Resetting the Active Surveillance Clock: Apalutamide in Lower Risk Prostate Cancer. Oral Presentation at: 2020 Society of Urologic Oncology Annual Meeting. Virtual

4. Graham L, Reder N, Gulati R, Grivas P, Wright J, Yu E, Hou W, Nega K, Yezefski T, Montgomery RB, Mostaghel E, Ellis W, True L, Lin DW, Nelson P, **Schweizer MT**. Targeting Backdoor Androgen Synthesis Through AKR1C3 Inhibition: A Presurgical Hormonal Ablative Neoadjuvant Trial in High Risk Localized Prostate Cancer (PC). Poster presented at: 2019 ASCO Annual Meeting, Chicago, IL.

5. **Schweizer MT**, Haugk K, Cheng H, Dumpit R, Nelson PS, Montgomery RB, Plymate SR, Yu EY. Challenges in Enrolling to Metastatic Castration-Resistant Prostate Cancer (mCRPC) Studies that Require Androgen Receptor Splice Variant (AR-V) Positivity. Poster presented at: 2017 Genitourinary Cancers Symposium, Orlando, FL

6. **Schweizer MT**, Wang H, Luber B, et al. Bipolar Androgen Therapy (BAT) in Men with Hormone Sensitive (HS) Prostate Cancer (PC). Poster presented at: 2016 Genitourinary Cancers Symposium, San Francisco, CA.

7. **Schweizer MT**, Antonarakis ES, Wang H, et al. A Pilot Study of Parenteral Testosterone and Oral Etoposide in Men with Castrate-Resistant Prostate Cancer. Poster presented at: 2014 ASCO Annual Meeting, Chicago, IL.

8. **Schweizer MT**, Antonarakis ES, Wang H, et al. A Pilot Study of Parenteral Testosterone and Oral Etoposide in Men with Castrate-Resistant Prostate Cancer. Poster presented at: 2014 ASCO Genitourinary Cancers Symposium, San Francisco, CA.

9. **Schweizer MT**, Zhou XC, Wang H, et al. The Effect of Prior Abiraterone Treatment on Subsequent Response to Docetaxel in Men with Metastatic Castrate-Resistant Prostate Cancer (CRPC). Poster presented at: 2014 ASCO Genitourinary Cancers Symposium, San Francisco, CA.

10. **Schweizer MT**, Huang P, Sternberg CN, De Wit R, Ecstein-Fraisse EB, Kattan MW, Kibel AS, Eisenberger, MA. Prospective evaluation of testosterone (T) recovery and PSA relapse following 18 months of androgen deprivation (ADT) after prostatectomy (RP): Results from the TAX-3501 trial. J Clin Oncol 31, 2013 (suppl; abstr 5023). Poster discussion presented at: 2013 ASCO Annual Meeting, Chicago, IL.

11. **Schweizer MT**, Bardia A, Blackford A, Lin J, Armstrong AJ, King A, Rudek MA, Yegnasubramanian A, Carducci MA. A Prostate Cancer Clinical Trials Consortium Trial of Disulfiram (D) in Men with Non-metastatic Recurrent Prostate Cancer (PCa). J Clin Oncol 31, 2013 (suppl 6; abstr 219). Poster presented at: 2013 ASCO Genitourinary Cancers Symposium, Orlando, FL.

12. **Schweizer MT**, Zhou XC, Wang H, Yang T, Shaukat F, Eisenberger MA, Antonarakis ES. Metastasis-Free Survival (MFS) is Associated with Overall Survival (OS) in Men with PSA-Recurrent Prostate Cancer Treated with Deferred Androgen Deprivation Therapy. J Clin Oncol 31, 2013 (suppl 6; abstr 109). Poster presented at: 2013 ASCO Genitourinary Cancers Symposium, Orlando, FL.

13. **Schweizer MT**, Zhang Y, Kunnavakkam R, Karrison R, Le Beau MM, Larson RA. Detection of combinations of cytogenetic abnormalities in chronic lymphocytic leukemia (CLL) by fluorescent in situ hybridization (FISH) probes. J Clin Oncol 28:15s, 2010 (suppl; abstr 6591). Poster presented at: 2010 ASCO Annual Meeting, Chicago, IL.

16. Other:

2022	Speaker, Comprehensive UW Medicine Hematology & Oncology Review Course, *Prostate Cancer*, Seattle, WA. September, 2022.
2022	Speaker, 2022 ASCO Annual Meeting, *Innovative Immune Approaches in Prostate Cancer: A Case-Based Review of CAR T, T cell Engagers, and Next-Generation Agents*, Chicago, IL. June 6, 2022
2021	Speaker, 21st Annual Pacific NW Prostate Cancer Conference, *Changing Landscape of Metastatic Prostate Cancer*, Virtual. October 2, 2021
2021	Speaker, Comprehensive UW Medicine Hematology & Oncology Review Course, *Prostate Cancer*, Virtual. June, 2021.
2021	Speaker, Society for Immunotherapy of Cancer: Advances in Cancer Immunotherapy, *Immunotherapy for the Treatment of Genitourinary Malignancies*, Virtual. April 2, 2021.
2020	Speaker, Society of Urologic Oncology Annual Meeting, *Resetting the Active Surveillance Clock: Apalutamide in Lower Risk Prostate Cancer*, virtual meeting. December 3, 2020
2020	Speaker, Medscape CME*, Immune Checkpoint and PARP Inhibitors in Prostate Cancer*, virtual. December 2020
2020	Speaker, Opinions in Genitourinary Malignancies Global Summit, *Great Debates in GU Malignancies*, virtual. September 28, 2020
2020	Speaker, Opinions in Prostate Cancer: An Interactive Workshop, *Genomic Testing and Interpretation*, virtual. August 25, 2020
2020	Speaker, Community Opinions in Prostate Cancer, *Patient and Disease Characteristics that Influence Treatment Selection in mCSPC*, Seattle, WA. March 3, 2020

2019 Speaker, 26th Annual Prostate Cancer Foundation Scientific Retreat. *FGFR-inhibition in Double Negative Prostate Cancer: Rationale and Future Directions,* Carlsbad, CA. October 25, 2019

2019 Speaker, 5th Annual Men's Health Update. *Prostate Cancer: A Lifelong Disease*, Seattle, WA. August 23, 2019

2019 Speaker, Gordon's Research Conference: Hormone-dependent Cancers. *Targeting Prostate Cancer Drug Resistance*, Newry, ME. August 7, 2019

2019 Keynote Speaker, Brotman Baty Institute for Precision Medicine: Cell-free DNA Symposium, *Applications of cfDNA in Prostate Cancer*, Seattle, WA. April 17, 2019.

2019 Speaker, UWMC Chief of Medicine Conference, *Germ Cell Tumors/Testicular Cancer*, Seattle, WA. March 19, 2019

2019 Speaker, Selected Topics in Hematology / Oncology Fellow's Lecture Series, *Bladder Cancer*, Seattle, WA. March 15, 2019

2019 Speaker, Nuclear Medicine Topical Conference, *Prostate Cancer 101*, Seattle, WA. March 12, 2019.

2019 Speaker, Prostate Cancer SPORE Seminar, *Targeting Backdoor Androgen Synthesis vis AKR1C3 Inhibition,* Seattle, WA. February 28, 2019

2019 Speaker, Skagit Valley Hospital, *Emerging Therapies in Cancer: New Treatments for Prostate Cancer*, Mt Vernon, WA. February 27, 2019

2019 Speaker, VA Puget Sound Health Care System, *Oncologic Emergencies*, Seattle, WA. February 26, 2019.

2018 Speaker, Cancer Immunotherapy Trial Network Meeting, *CDK12 Mutation as a Biomarker for Response to Immune Checkpoint Blockade*, Washington, D.C. November 7, 2018.

2018 Speaker, Society for Immunotherapy of Cancer: Advances in Cancer Immunotherapy, *Immunotherapy for the Treatment of Genitourinary Malignancies*, Seattle, WA. November 3, 2018.

2018 Speaker, Fred Hutchinson Cancer Research Center Grand Rounds, *Targeting Prostate Cancer Drug Resistance*, Seattle, WA. October 2, 2018.

2018 Speaker, Society of Utah Medical Oncologists, *Urothelial Carcinoma: Updates and Future Directions*, Park City, UT. September 22, 2018.

2018 Speaker, Prostate Cancer SPORE Seminar, *PNW Prostate Cancer Clinical Trials Overview: UW/SCCA,* Seattle, WA. September 6, 2018

2018 Speaker, Comprehensive UW Medicine Hematology & Oncology Review Course, *Systemic Therapy In The Treatment of Bladder Cancer*, Seattle, WA. September 15, 2018.

2018 Speaker, Fellow Research Flash Rounds, *Translational Prostate Cancer Research*, Seattle, WA. July 31, 2018.

2018 Speaker, University of Utah: Huntsman Cancer Institute Genitourinary Oncology Symposium, *MSI-high Prostate Cancer: Finding the Needle in the Haystack*, Salt Lake City UT. May 25, 2018

2018 Speaker, University of Utah: Huntsman Cancer Institute Translational Oncology Seminar, *High-dose Testosterone Therapy for Prostate Cancer: Biomarkers and Combination Strategies*, Salt Lake City UT. May 24, 2018.

2018 Speaker, Institute for Prostate Cancer Research Symposium, *Improving Survival with Combination Therapy*, Seattle, WA. April 28, 2018.

2018 Speaker, City of Hope: Special Lecture, *Prostate Cancer: Histologic Subtypes and Molecular Correlates*, Duarte, CA. January 18, 2018.

2017 Speaker, CCSG Retreat, *State of Research: Clinical Trials*, Seattle, WA. November 9, 2017.

2017 Speaker, Everett Clinic, *Evolving Options for GU Cancer*s, Everett, WA. November 6, 2017

2017 Speaker, Selected Topics in Hematology / Oncology Fellow's Lecture Series, *Systemic Therapy in the Treatment of Bladder Cancer*, Seattle, WA. October 20, 2017.

2017 Speaker, Prostate Cancer Clinical Trials Consortium, *High-dose Testosterone Plus PARP Inhibition in mCRPC*, teleconferenced nationally. August 29, 2017.

2017 Speaker, Comprehensive UW Medicine Hematology & Oncology Review Course, *Systemic Therapy in The Treatment of Bladder Cancer*, Seattle, WA. September 25, 2017.

2017 Speaker, SWOG GU Organ Site Meeting: Prostate Organ Site, *Bipolar Androgen Therapy for Metastatic Castration-Resistant Prostate Cancer*, San Francisco, CA. April 28, 2017.

2017 Speaker, Prostate Cancer Clinical Trials Consortium, *Durvalumab in MSI-high CRPC*, teleconferenced nationally. April 20, 2017.

2017 Speaker, Institute for Prostate Cancer Research Symposium, *Liquid Tumor Biopsies to Guide Precision Medicine*. Seattle, WA. March 18, 2017.

2017 Speaker, Fred Hutchinson Cancer Research Center Grand Rounds, *High-dose Testosterone to Treat Prostate Cancer*, Seattle, WA. January 31, 2017.

2016 Speaker, Selected Topics in Hematology / Oncology Fellow's Lecture Series, *Systemic Therapy in the Treatment of Bladder Cancer*, Seattle, WA. December 30, 2016.

2016 Speaker, Department of Medicine Core Teaching Conference, *Prostate Cancer: Screening and Beyond*, Seattle, WA. October 17, 2016.

2016 Speaker, Prostate Cancer SPORE Seminar, *Immunotherapy in Hypermutated Prostate Cancers*, Seattle, WA. September 29, 2016.

2016 Speaker, Comprehensive UW Medicine Hematology & Oncology Review Course, *Systemic Therapy in The Treatment of Bladder Cancer*, Seattle, WA. September 24, 2016.

2016 Speaker, Prostate Cancer SPORE Seminar, *A Phase I Study of Niclosamide in Combination with Enzalutamide in Men with Androgen Receptor Splice Variant Positive Castration- Resistant Prostate Cancer*, Seattle, WA. July 28, 2016.

2016 Speaker, Institute for Prostate Cancer Research Symposium, *Cancer Immunology 101,* Seattle, WA. April 30, 2016.

2015 Speaker, Comprehensive UW Medicine Hematology & Oncology Review Course, *Systemic Therapy in The Treatment of Bladder Cancer*, Seattle, WA. September 27, 2015

2015 Speaker, Comprehensive UW Medicine Hematology & Oncology Review Course, *Germ Cell Tumors/Testicular Cancer*, Seattle, WA. September 27, 2015

2015 Speaker, Coffey-Holden Prostate Cancer Academy Meeting, *Moving Chemotherapy Earlier in the Disease Process*, La Jolla, CA. June 26, 2015.

2015 Speaker, Institute for Prostate Cancer Research Symposium**,** *Testosterone Therapy: Science, Rationale and Caution*, Seattle, WA. April 11, 2015.

2015 Speaker, Prostate Cancer SPORE Seminar, *Old Drugs, New Tricks: Repurposing Approved Drugs to Treat Prostate Cancer*, Seattle, WA. February 5, 2015.

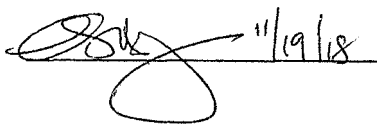
2014 Speaker, Annual Multi-Institutional Prostate Cancer Program Retreat, *A Pilot Study of Supraphysiologic Testosterone and Oral Etoposide in Men with Castrate-Resistant Prostate Cancer*, Fort Lauderdale, FL. March 17, 2014.

1. Schweizer, M.T., Penkov, K.D., Tolcher, A.W., Choudhury, A.D., Doronin, V., Aljumaily, R., Calvo, E., Frank, R.C., Hamm, J.T., Moreno Garcia, V., Vorobyev, V., Billotte, S., Bowler, T., Chen, J., Lin, T., Liu, L., Maity, A., Sharma, S. & Johnson, M.L. Phase I trial of PF-06821497, a potent and selective inhibitor of enhancer of zeste homolog 2 (EZH2), in follicular lymphoma (FL), small cell lung cancer (SCLC) and castration-resistant prostate cancer (CRPC). in *ESMO Congress* (Paris, France).

November 16, 2018

CURRICULUM VITAE

Celestia S. Higano, MD, FACP
Professor of Medicine and Urology, University of Washington School of Medicine
Member, Fred Hutchinson Cancer Research Center
Seattle Cancer Care Alliance
825 Eastlake Avenue East, G4-830
Seattle, WA 98109
Phone: (206) 606-1152
Email: thigano@u.washington.edu



EDUCATION

Undergraduate

Bryn Mawr College Bryn Mawr, Pennsylvania	1970-1971
Clark University Worcester, Massachusetts	1972-1975

Medical

University of Massachusetts Worcester, Massachusetts	1975-1979

Post Graduate

Internal Medicine Residency Mayo Graduate School of Medicine Rochester, Minnesota	1979-1982
Hematology/Oncology Fellowship University of Washington Seattle, Washington	1982-1984
AACR/ASCO Clinical Trials Graduate Workshop Vail, Colorado	1998
ASCO Leadership Seminar Alexandria, Virginia	2011

FACULTY APPOINTMENTS

Acting Instructor, Department of Medicine School of Medicine, University of Washington	1984-1988
Acting Assistant Professor, Department of Medicine School of Medicine, University of Washington	1988-1989
Associate in Clinical Research Fred Hutchinson Cancer Research Center	1988-2008
Assistant Professor, Department of Medicine School of Medicine, University of Washington	1989-1997
Associate Professor, Department of Medicine School of Medicine, University of Washington	1997-2008
Adjunct Associate Professor, Department of Urology School of Medicine, University of Washington	1997-1999
Associate Professor, Department of Urology School of Medicine, University of Washington	1999-2008
Professor, Department of Medicine School of Medicine, University of Washington	2008-present

Professor, Department of Urology School of Medicine, University of Washington	2008-present
Member, Clinical Research Division Fred Hutchinson Cancer Research Center	2008-present
Affiliate Member, Dept of Urologic Sciences University of British Columbia	2013-present
Medical Director, Prostate Cancer Supportive Care Program Vancouver Prostate Centre, Vancouver General Hospital	2013-present

TRAINEES (last 5 years)

Jennifer Bossio, PhD	2015-present
Lindsay Hedden, PhD	2015-present
Evandro Bezerra, MD	2017-present
Sarah Weller, MSc Candidate	2017-present

HONORS AND AWARDS

National Honor Society	1969
Phi Beta Kappa	1975
Lange Award, Outstanding Medical Student	1979
American Medical Writers Association	2005
America's Top Doctors List	2005 – present
Alpha Omega Alpha	2007
Fellow, American College of Physicians	2008
Prostate Cancer Challenge Award	2011
Forbes Distinguished Alumni Award, Bancroft School	2015
Top Cancer Doctors Award, Newsweek	2015
National Association of Professional Women, VIP Woman of the Year	2015-2016

BOARD CERTIFICATION

American Board of Internal Medicine	1982
Medical Oncology	1985

MEDICAL LICENSES

Minnesota	1979-1982
Washington	1982-present
California	2010-present

PROFESSIONAL ORGANIZATIONS

American Association for Cancer Research	1992-present
American Society of Clinical Oncology	1985-present
Puget Sound Oncology Consortium	1994-2015
American Society of Hematology	1994-present
American Urological Association	1997-present
Society of Women in Urology	1996-present
Southwest Oncology Group	1985-present
The Society of Urologic Oncology	2002-present
European Society for Medical Oncology	2013-present
Washington State Medical Association	1985-present
Washington State Medical Oncology Society	1999-present
Washington State Prostate Cancer Coalition	2002-present

EDITORIAL BOARDS

American Cancer Society
Clinical Care for Prostatic Disease
Clinical Genitourinary Cancer
Clinical Prostate Cancer
Journal of Clinical Oncology

NATIONAL RESPONSIBILITIES

American Society of Clinical Oncology (ASCO)	
Scientific Program Committee	2003-2005
Scientific Program Committee, ASCO Prostate Cancer Symposium	2004-2005
American College of Radiology Appropriateness Criteria Panel Member	2005-2008
Ad Hoc ASCO Prostate Cancer Guideline Review Panel	2006
Candidate for ASCO Nominating Committee	2008
Cancer Education Committee – Genitourinary Cancer Track	2008-2011
Candidate for Nominating Committee	2014
Member, Continuing Education Committee	2015-present
Chair, Continuing Education Ccommittee	2017-2018
American Urological Association (AUA)	
Treatment of Localized Prostate Cancer Consensus Committee	2001
External peer reviewer for Localized Prostate Cancer Treatment Guidelines	2016
American Association of Cancer Research (AACR)	
Scientific Program Committee, 2018 AACR Annual Meeting	2017-2018
Society of Urologic Oncology (SUO)	2003
Consensus Panel on Hormone Refractory Prostate Cancer	
Southwest Oncology Group (SWOG)	
Oncology Discipline Chair, Genitourinary Committee	1993-present
Endpoints Review Committee, Prostate Cancer Prevention Trial	1998-2004
Specialized Program of Research Excellence in Prostate Cancer (SPORE)	
Pacific Northwest PC SPORE Clinical Core Director	2002-2012
Co-chair, InterSPORE Clinical Trials Concept Review Committee	2002-2005
National Comprehensive Cancer Network (NCCN)	
Member, Prostate Cancer Guidelines Panel	2010-present
NCCN/VA CRPC Curriculum Development Committee	2015
Panel Member, Value Pathways Task Force	2018-
National Cancer Institute (NCI)	
Member, SxQOL Drug Development Task Force	2008-2015
Prostate Cancer Working Group (PCWG)	
PSA Working Group	2001-2004
PCWG 2	2004-2008
PCWG 3	2011-2016
Prostate Cancer Foundation (PCF)	
Standing Review Committee	2010-present
PCF-Canada ASAP 2012	2012
PCF-Australia/Movember MRTA-3 review panel member	2012
PCF-Canada/Movember Transformational Science Award reviewer	2017

Eastern Cooperative Oncology Group Reverse Site Visit	2003
American Joint Committee on Cancer Genitourinary Task Force	2005-2007
West Hawaii Cancer Symposium Co-Chair and Co-organizer	2000-present
Treatment and the Focal Lesion Paradigm Consensus Panel Member, International Task Force on Prostate Cancer	2005-2006
International Bisphosphonate Summit Meeting Chair and Organizer	2002
UpToDate in Oncology: Peer Review Board	2005-2006

INDEPENDENT DATA SAFETY MONITORING BOARDS

Member, 2 Millenium phase 3 trials	2010-2014
Member, SOTIO phase 3 trial	2014-present
Member, Alliance Foundation Trials (AFT)	2016-present
Member, Movember GAP 4 (INTERVAL)	2016-present
Chair, Advantagene phase 3 trial	2016-present

SCIENTIFIC STEERING COMMITTEES

Cell Genesys GVAX Steering Committee, global PI for VITAL 1 phase 3	2008-2009
Cougar Biotech (Abiraterone Acetate) Steering Committee	2008-2010
AstraZeneca (ENTHUSE/zibotentan) Steering Committee, global PI for phase 3	2008-2012
Medivation (STRIVE) Steering Committee	2010-2015
Dendreon (PROCEED Registry) Steering Committee	2010-present
Teva (OGX-011 Custirsen) Steering Committee, global co-PI with Chi and de Bono	2011-2016
Bayer Xofigo (REASSURE Registry) Steering Committee	2011-present
Bayer RA 223 Phase 3 Steering Committee, global co-PI with Matthew Smith	2013-present
MorphoSys (MOR209) Steering Committee	2011-present
Ferring (PRONOUNCE) Steering Committee	2015-present
Pfizer talazoparib phase 2 Steering Committee	2016-present
Clovis (TRITON) Steering Committee	2016-present
Pfizer Talazoparib Steering Committee	2017-presnet

SCIENTIFIC ADVISORY BOARDS since 2010

Amgen (XGEVA denosumab) Advisory Board	2008-2011
Medivation (PREVAIL) Advisory Board	2010-2014
Bristol-Myers Squibb (IDEA) Advisory Board	2011
Genentech Prostate/Bladder Advisory Board	2011
Orion (ODM-201) Advisory Board	2012
Novartis – Prostate Cancer Advisory Board	2012
Dendreon Sequencing Therapy Advisory Board	2012
Veridex Steering Committee	2012-2013
Dendreon Data Mining/PDAAC	2013
Johnson & Johnson Cellsearch Advisory Board	2013
AbbVie – Lupron Advisory Board	2013
Ferring – Firmagon Intermittent Therapy	2013
BHR – Estragel Advisory Board	2014
Astellas (XTANDI) Advisory Board	2014-2016
Astellas Global Medical Affairs Advisory Board	2015

Churchill Prostate Cancer Advisory Board	2015
Emergent (STRIVE/TERRAIN) Advisory Board	2015-2016
Blue Earth Diagnostics Advisory Board	2015-present
Dendreon Advisory Board	2016
Endocyte Advisory Board	2016-present
Asana BioSciences Advisory Board	2016-present
Orion Advisory Board	2017-present

LOCAL RESPONSIBILITIES

State of Washington

American Cancer Society, Northwest Chapter	1998-2002
Washington State Prostate Cancer Coalition Task Force	2002-present

University of Washington/Fred Hutchinson

Institute for Prostate Cancer Research Committee	1999-2014
Sponsored Programs/Human Subjects Faculty Advisory Committee	2004-2006
Research Trials Office Oversight Committee	2002-2006

University of Washington Search Committees:

Associate Director of Clinical Research Division	2002-2005
Phase I Clinical Trials Director of Medical Oncology	2006-2007
Renal/Melanoma Faculty	2007-2008
Lung and Head and Neck Faculty	2008-2010

Seattle Cancer Care Alliance

Joint Oncology Planning Committee, GU Patient-Care Subcommittee	1999-2001
Space Planning Committee	2008-2010
SCCA Strategic Planning Committee	2008-2009

COMMUNITY SERVICE

Eastside Prostate Cancer Support Group	1997-present
Bellevue Rotary Club	1997
American Cancer Society, Northwest Chapter, Prostate Cancer Task Force	1998-2006
Northwest Hospital Prostate Cancer Support Group	1998
Northwest Prostate Cancer Foundation	2000
Washington State Prostate Cancer Coalition	2002-present
Tacoma Prostate Cancer Support Group	2006
UsTOO in Seattle	2010-present

INVITED TALKS AND LECTURES SINCE 2012

UNIVERSITY/LOCAL

1. Fred Hutchinson Cancer Research Center's 2nd Symposium on Cancer Survivorship for Clinicians: Monitoring and Managing the Side Effects of Adrogen Deprivation Therapy for Prostate Cancer. Seattle, WA. February 2012.
2. "New approaches to androgen deprivation therapy", Virginia Mason GU Tumor Board, Virginia Mason Medical Center. Seattle, October 2012.
3. 12th Annual Pacific Northwest Prostate Cancer Conference, Seattle, WA. October 2012.
4. "Immunotherapy for Prostate Cancer", IPCR Symposium, Fred Hutchinson Cancer Research Center, Seattle, March 2013.
5. "Beyond hormonal therapy", PNW Prostate Cancer SPORE Retreat, Seattle, July 2013.

6. 13th Annual Pacific Northwest Prostate Cancer Conference, Seattle, September 2013.
7. PNW Prostate Cancer SPORE Retreat, Seattle, July 2014.
8. 14th Annual Pacific Northwest Prostate Cancer Conference, Seattle, September 2014.
9. "New Treatments on the Horizon" 15th Annual Pacific Northwest Prostate Cancer Conference, Seattle, September 2015.
10. "Androgen deprivation therapy and cardiovascular risk: What's the real story?" Fred Hutchinson Cancer Research Center, Grand Rounds, Seattle, April, 2016.
11. "Hormone therapy and cardiovascular risk: What do we know?" 16th Annual Pacific Northwest Prostate Cancer Conference, Seattle, September, 2016.

NATIONAL/INTERNATIONAL

1. ASCO GU Satellite Symposium. "Sequencing of New and Emerging Agents in mCRPC." San Francisco, CA. February 2012.
2. Fresenius Kabi AG, FORCE Meeting: The Evolving Treatment Paradigm for Castration Resistant Prostate Cancer. "Advances in supportive care for cancer management." Ho Chi Minh City, Vietnam. February 2012.
3. Fresenius Kabi AG, FORCE Meeting: Monitoring and Managing the Side Effects of Androgen Deprivation Therapy for Prostate Cancer. "Management of PSA Recurrent." Ho Chi Minh City, Vietnam. February 2012.
4. Clinical Care Options Satellite Symposium. "Metastatic prostate cancer case: Skeletal related events". ASCO Annual Meeting. Chicago, IL. June 2012.
5. Chinese Society of Clinical Oncology. "Optimal hormonal therapy for metastatic prostate Cancer" and "Current standard of practice after ASCO 2012: the evolving treatment paradigm prostate cancer". Best of ASCO China, Nanjing, China. July 2012.
6. Best of ASCO Satellite Symposium: Pathways to Progress in Castration-Resistant Prostate Cancer and Renal Cell Carcinoma: Practical Guidance for Clinicians. "Androgens still matter in castration resistant prostate cancer: targeting androgen signaling beyond castration resistance." San Diego, CA. August 2012.
7. 15th Annual West Hawaii Cancer Symposium. "Health Care Reform and Clinical Trials." Kailua-Kona, HI. September 2012.
8. MD Anderson Cancer Center Comprehensive Board Review Course. "Prostate Cancer 2012" Houston, TX. September 2012.
9. "Novel immunotherapeutic approaches in metastatic castration resistant prostate cancer". GU ASCO Satellite Symposium: Castration-Resistant Prostate Cancer, Important Questions, Encouraging Answers. Orlando, FL. February 2013.
10. "Leveraging the immune system in prostate cancer". GU ASCO Satellite Symposium: Research to Practice Symposium: A Live Investigator Think Tank. Orlando, FL. February 2013.
11. Gold Journal (*Urology*) Roundtable Resource Center. "Immunotherapy in clinical practice." Chicago, IL. February 2013. Urology on line http://education.goldjournal.net/path.php?1396:0:Media:title:bxvcs
12. "Latrogenic side effects of androgen deprivation therapy: a practical clinical approach" and "Systemic management of CRPC, Panel discussion". Issues and Controversies in Prostate Care 2013: Review of prostate cancer clinical trials. Whistler, BC. March 2013.
13. ASCO Satellite Symposium: The Team Quiz Challenge: Bone Modifying Agents in the Treatment of Cancer. Program Director. "Metabolic and skeletal complication of androgram deprivation therapy." Chicago, IL. June 2013.
14. ASCO Satellite Symposium: Modern management of metastatic castration-resistant prostate cancer in 2013 and beyond: navigating the successes, hurdles, and practicalities. "Immunotherapy for Advanced Prostate Cancer: Current status and future potential." Chicago, IL. June 2013.
15. ASCO Education Session, Androgen Deprivation Therapy for Prostate Cancer. "Metabolic and skeletal complications of androgen deprivation therapy." Chicago, IL. June 2013.

16. "Intermittent androgen deprivation: Recommendations." NCCN Prostate Cancer Panel meeting. Philadelphia, PA. June 2013.

17. "Prostate cancer 2013: a case based review", 23rd Annual Mayo Clinic Hematology Oncology Reviews, Amelia Island, FL. August 2013.

18. "New Treatment Options for Metastatic Prostate Cancer", 16th Annual West Hawaii Cancer Symposium, Kailua-Kona, HI. September 2013.

19. "Holistic Approach to PCa Therapy: A Multidisciplinary Opportunity." Chair, AbbVie Advisory Board. Vancouver, BC. September 2013.

20. "Overall survival benefit with Radium-223: Pre and post docetaxel." and "Novel immunotherapeutic approaches in Prostate Cancer." 1st International State-of-the-Art Uro-Oncology Conference on Prostate and Kidney Cancers, EUOG, Amsterdam, Netherlands. September 2013.

21. "Identifying common molecular features of ERG positive tumors in primary and castration-resistant prostate cancer", Annual Prostate Cancer Foundation Retreat, National Harbor MD. October 2013.

22. "Real-world experience with Sipuleucel-T in metastatic castration-resistant prostate cancer (mCRPC) patients (pts) ≥80 years-old: data from PROCEED", Western AUA Conference, Monterey CA. November 2013.

23. "Use of intermittent androgen deprivation therapy based on mathematical modeling of PSA and other parameters", Mathematical Modeling Workshop, Institute of Industrial Science, University of Tokyo Japan. December 2013.

24. "Non-hormone Therapy for Metastatic Castration-Resistant Prostate Cancer: Chemotherapy, Bone-Targeted Treatments and Others", Scripps 34th Annual Conference of Clinical Hematology & Oncology, San Diego CA. February 2014.

25. "Advancing the Standard of Cancer Care: New Developments in the Treatment of Hormone Refractory Prostate Cancer", NCCN Annual Meeting, Fort Lauderdale, Florida. March 2014.

26. "Radium-223 for the treatment of metastatic castration resistant prostate cancer." ERA-223 Investigator Meeting. San Diego, CA. April 2014.

27. "On the Shoulders of Giants – Prostate Cancer Therapy: How Did We Get Here and Where Are We Going" Topic: Immunotherapy for Prostate Cancer, ASCO Annual Meeting, Chicago. May 2014.

28. "New developments in the treatment of metastatic castration resistant prostate cancer." And "The evolving role of chemotherapy for metastatic castration resistant prostate cancer." Mexican Urologic Oncology Society Annual Meeting. Acapulco, Mexico. July 2014.

29. MD Anderson Cancer Center Comprehensive Board Review Course. "Prostate Cancer 2014" Houston, TX. September 2014.

30. "Effect of prior abiraterone or enzalutamide on sipuleucel-T manufacture in PROEED Registray patients." Western Section AUA Meeting. Maui, HI. October 2014.

31. Movember Foundation Revolutionary Team 3 Award Grant Review. Panel member. Sydney Australia. November 2014.

32. "Prostate Cancer, a glance at the near future." 1st International Geriatric Oncology Meeting. Rome, Italy. December 2014.

33. "Advanced Prostate Cancer: using Sip-T first in mCRPC", Dendreon National Sales Meeting, Santa Barbara, CA. January 2015.

34. ASCO CME Committee meeting. Alexandria, VA. February 2015.

35. "Novel Therapies: Radiopharmaceuticals for Castration-Resistant Prostate Cancer", New York GU, 8th Annual Interdisciplinary Congress, New York, NY. March 2015.

36. Panelist for the OncLive TV Peer Exchange Channel. Expert Panel Discussion: "Management of mCRPC; A Practical Review of Guideline Updates and Case Study Perspectives" (video). New Orleans, LA. May, 2015

37. "STRIVE, A Multicenter Phase 2 Study of Enzalutamide versus Bicalutamide in Men with Nonmetastatic or Metastatic Castration-Resistant Prostate Cancer." AUA Annual Meeting, Plenary Session. New Orleans, LA. May 2015.

38. ASCO Post Interviewer. ASCO Annual Meeting, Chicago, IL. June 2015

39. "Advances in hormonal therapy for prostate cancer over the last five years." Regional Summit on Practical and Emerging Trends in Genitourinary Malignancies, San Francisco, CA. June 2015.

40. "Implementation of the Prostate Cancer Supportive Care Program, A Comprehensive Approach for Men with Prostate Cancer and Their Partners." Multinational Association of Supportive Care in Cancer Annual Meeting. Copenhagen, Denmark. June 2015.

41. "Radium 223 Benefit in Castration Resistant Prostate Cancer", 33rd National Congress in Oncology, Mexican Society of Oncology. Cancun, Mexico. October 2015.

42. "Changing landscape in early castration-resistant prostate cancer." Astellas Advisory Board Meeting. Budapest, Hungary. November 2015.

43. FDA "Type A" Meeting (Churchill Pharma). Silver Spring, MD. November 2015.

44. "Androgen Deprivation Therapy: What's the real story about cardiovascular risk?", Provincial Tumour Group Meeting. Vancouver, Canada. November 2015.

45. Movember Prostate Cancer Outcomes: Global Initiative to Compare and Reduce Variation. Delegate. Culver City, CA. December 2015.

46. "Analysis of the PROCEED registry by baseline prostate-specific antigen (PSA) quartiles: Preliminary analysis of real-world sipuleucel-T (sip-T) use." Poster presentation. ASCO-GU Symposium. San Francisco, CA. January 2016.

47. Session 7: Testicular Cancer. Session Monitor. ASCU-GU Symposium. San Francisco, CA. January 2016.

48. "Successful implementation of a disease-specific survivorship program for men with prostate cancer (PC) and their partners." Poster presentation. 2016 Cancer Survivorsip Symposium: Advancing Care and Research. San Francisco, CA. January 2016.

49. "Utilization of sexual health and pelvic floor physiotherapy services in Vancouver's Prostate Cancer Supportive Care (PCSC) Program. 2016 Cancer Survivorship Symposium: Advancing Care and Research. San Francisco, CA. January 2016.

50. "Management of metastatic prostate cancer." Mayo Clinic: Clinical and Multidisciplinary Hematology and Oncology 2016 13th Annual Review. Scottsdale, AZ. January 2016.

51. ASCO CME Subcommittee Meeting. Alexandria, VA. February 2016.

52. "Integrating immunotherapy in the management of metastatic castration resistant prostate cancer." And "Challenging Case Debates." New York GU, 9th Annual Interdisciplinary Congress, New York, NY. March 2016.

53. "Prostate Cancer: A Discussion of the Latest Developments to Change Care in the Oncology Clinic." Program Director: Optimizing the Treatment of Advanced Prostate Cancer: Expert Review of the Latest Data and Guideline Recommendations. CCO/ NCCN Satellite Symposium at ASCO. Chicago, IL. June 2016.

54. "Utilization of sexual health and pelvic floor physiotherapy services in Vancouver's Prostate Cancer Support Care Program." Poster presentation. ASCO Annual Meeting. Chicago, IL. June 2016.

55. Prostate Cancer Co-chair. 2nd RIMOG New and Emerging Therapeutic Options in Geriatric Oncology Meeting. Florence, Italy. July 2016.

56. "Arv-7 Story and clinical implications." 17th Asia-Pacific Prostate Cancer Conference. Melbourne, Australia. August/September, 2016.

57. "ADT and Cardiovascular Risk." 17th Asia-Pacific Prostate Cancer Conference. Melbourne, Australia. August/September, 2016.

58. "Successful Implementation of a Prostate Cancer Survivorship Program." 17th Asia-Pacific Prostate Cancer Conference. Melbourne, Australia. August/September, 2016.

59. "Pain and the Prostate Cancer Patient." 17th Asia-Pacific Prostate Cancer Conference. Melbourne, Australia. August/September, 2016.

60. MD Anderson Cancer Center Comprehensive Board Review Course. "Prostate Cancer 2016" Houston, TX. September 2016.

61. Module 2: "Sequence and Selection of Secondary Hormonal Therapy, Immunotherapy and Cytotoxic Therapy for Patients with mCRPC", Research to Practice Satellite Symposium - Cases from the Community: Clinical Investigators Provide their Perspectives on Emerging Research and Actual Patients with Advanced Prostate Cancer. Orlando, FL. February, 2017.

62. "The changing landscape of metastatic castration-resistant prostate cancer." Genentech Grand Rounds. San Francisco, CA. February 2017.

63. "Updagte of On-going phase 3 trials in metastatic hormone sensitive prostate cancer." 2nd Advanced Prostate Cancer Consensus Conference (APCCC). St. Gallen, Switzerland. March, 2017.

64. "Isotope therapy and PARP inhibitors for advanced prostate cancer." and "Case debates: best practices." New York GU, 10th Annual Interdisciplinary Congress, New York, NY. March 2017.

65. "Best practices for the management of metastatic castration-resistant prostate cancer across the disease continuum." Practicing Clinicians Exchange (PCE) Symposium. Anaheim, CA. March 2017.

66. "Personalized sequencing in castration-resistant prostate cancer." PER Medical Crossfire Symposia. Chicago, IL. June 2017.

67. "The changing treatment landscape for metastatic castration-resistant prostate cancer"and "Considerations for sequencing of therapy for metastatic castration resistant prostate cancer." Japanese Society of Medical Oncology. Kobe, Japan. June 2017.

68. "The changing landscape ofmetastatic prostate cancer over the last 20 years." West Hawaii Cancer Symposium. Kona, HI. September 2017.

69. MD Anderson Cancer Center Comprehensive Board Review Course. "Prostate Cancer" Houston, TX. September 2017.

70. "Updates in Prostate Cancer: New Cancer Drugs." Seventh Annual Prostate Cancer Advocacy Symposium: A National Summit. Detroit, MI. September 2017.

71. "Treatment decisions in a new therapeutic landscape in men with mCRPC." Thai Society of Clinical Oncology Symposium. Bangkok, Thailand. November 2017.

72. "Focus on Safety Issues of Newer Hormonal Therapies." prIME Oncology CME-certified Symposium: Hormonal Therapy in Prostate Cancer: Improving Clinical Outcomes in Metastatic and Non-Metastatic Disease. San Francisco, CA. February 2018.

73. "Early Use of Systemic Therapy: Abiraterone Versus Docetaxel for Hormone-Sensitive Prostate Cancer." New York GU: 11th Annual Interdisciplinary Prostate Cancer Congress and Other Genitourinary Malignancies. New York, NY. March 2018.

74. "Prostate Cancer Disparities: Focus on African American Men." American Association for Cancer Research (AACR) Annual Meeting 2018. Chicago, IL. April 2018.

75. "Role of Data Monitoring Committees in Complicated Trials." Society for Clinical Trials (SCT) Annual Meeting. Portland, OR. May, 2018.

76. "Balancing Toxicities, and Therapeutics Perspective." 2018 ASCO Annual Meeting Session: Metastatic Prostate Cancer Tumor Board: Optimizing Patient Selection and Treatment. Chicago, IL. June 2018.

77. "Off Protocol Treatment of Oligometastatic Hormone Sensitive or CRPC Disease with SRRT." Asia-Pacific Prostate Cancer Conference (APPCC). Brisbane, Australia. August 2018.

78. "Implementation of an Electronic Patient Reported Outcome System in the Prostate Clinic at the Vancouver Prostate Centre." Asia-Pacific Prostate Cancer Conference (APPCC). Brisbane, Australia. August 2018.

79. "Hormone Sensitive Metastatic Disease: Treatment Options." Asia-Pacific Prostate Cancer Conference (APPCC). Brisbane, Australia. August 2018.

80. "New Options in MO CRPC – Who (if anybody) needs treatment." Asia-Pacific Prostate Cancer Conference (APPCC). Brisbane, Australia. August 2018.

81. "Current Data & Takeaways: Radium-223's Role as a Life-Prolonging Agent." ESMO 2018 Industry Satellite Symposium. Munich, Germany. October 2018.

82. "To Screen or Not to Screen – That is the Question." The University of Massachusetts Medical School Grand Rounds. Worcester, MA. October 2018.

83. "Biologic Rationale for Next-Generation AR Inhibitors." Global Summit on Genitourinary Malignancies. Banff, Canada. November 2018.

PEER-REVIEWED PUBLICATIONS

1. Tallman MS, McGuffin RW, Higano CS, Starkebaum G, Collins SJ, Johnston H, Singer JW, Perry DJ, Kunath A. Bone marrow transplantation in a patient with myelodysplasia associated with diffuse eosinophilic fascitis. *Am J Hematol.* 1987 24(1):93-99.

2. Abdel-Nabi HH, Schwartz AN, Higano CS, Wechter DG, Unger MW. Colorectal carcinoma: Detection with indium-111 anticarcinoembryonic-antigen monoclonal antibody ZCE-025. *Radiology.* 1987 164(3):617-621.

3. Livingston RB, Griffin BR, Higano CS, Laramore GE, Rivkin SE, Goldberg RS, Schulman SF. Combined treatment with chemotherapy and neutron irradiation for limited non-small cell lung cancer: A Southwest Oncology Group Study. *J Clin Oncol.* 1987 5(11):1716-1724.

4. Mortimer JE, Higano CS. Continuous infusion 5-fluorouracil and folinic acid in disseminated colorectal cancer. *Cancer Invest.* 1988 6(2):129-132.

5. Tallman MS, Nemunaitis JJ, McGuire TR, Yee GC, Hughes TE, Almgren JD, Appelbaum FR, Higano CS, McGuffin RW, Singer JW, Thomas ED. Comparison of two intravenous cyclosporine infusion schedules in marrow transplant recipients. *Transplantation.* 1988 45(4):810-813.

6. McGuire TR, Tallman MS, Yee GC, Nemunaitis JJ, Higano CS, McGuffin RW, Singer JW. Influence of infustion duration on the efficacy and toxicity of intravenous cyclosporine in bone marrow transplant patients. *Transplant Proc.* 1988 20(3 Suppl 3):501-504.

7. Russell KJ, Boileau MA, Ireton RC, Higano CS, Collins C, Koh WJ, Griffin BR, Chapman WH, Griffin TW. Transitional cell carcinoma of the urinary bladder: histologic clearance with combined 5-FU chemotherapy and radiation therapy. Preliminary results of a bladder-preservation study. *Radiology.* 1988 167(3):845-848.

8. Griffin BR, Livingston RB, Stewart GR, Higano CS, Russell KJ, Griffin TW, Laramore GE. Prophylactic cranial irradiation for limited non-small cell lung cancer. *Cancer.* 1988 62(1):36-39.

9. Collins C, Higano CS, Livingston RB, Griffin BR, Keppen MD, Miller TP. Cyclophosphamide, vincristine, cisplatin, VP-16 and radiation therapy in extensive small-cell lung cancer. A Southwest Oncology Group study. *Cancer Chemother Pharmacol.* 1989 24(2):128-132.

10. Higano CS, Livingston RB. Oral dipyridamole and methotrexate in human solid tumors: a toxicity trial. *Cancer Chemother Pharmacol.* 1989 23(4):259-262.

11. Jacobson AF, Cerqueira MD, Breitz HB, Whitley MA, Higano CS. Pleuroperitoneal communication associated with malignant ascites. A potential cause for new pleural effusion suggestive of pulmonary embolism. *Clin Nucl Med.* 1990 May; 15(5):317-320.

12. Bianco JA, Higano CS, Singer JW, Appelbaum FR, McDonald GB. The somatostatin analog octreotide in the management of the secretory diarrhea of the acute intestinal graft-versus-host disease in a patient after bone marrow transplantation. *Transplantation.* 1990 49(6):1194-1195.

13. Higano CS, Brixey M, Bryant EM, Durnam DM, Doney K, Sullivan KM, Singer JW. Durable complete remission of acute nonlymphocytic leukemia associated with discontinuation of immunosuppression following relapse after allogeneic bone marrow transplantation: A case report of a graft-versus-leukemia effect. *Transplantation.* 1990 50(1):175-177.

14. Bianco JA, Pepe MS, Higano CS, Appelbaum FR, McDonald GB, Singer JW. Prevalence of clinically relevant bacteremia following upper gastrointestinal endoscopy in bone marrow transplant recipients. *Am J Med.* 1990 89(2):134-136.

15. Russell KJ, Boileau MA, Higano CS, Collins C, Russell AH, Koh WJ, Cole SB, Chapman WH, Griffin TW. Combined 5-fluorouracil and irradiation for transitional cell carcinoma of the urinary bladder. *Int J Radiat Oncol Biol Phys.* 1990 19(3):693-699.

16. Abdel-Nabi HH, Schwartz AN, Wechter DG, Higano CS, Ortman-Nabi JA, Unger MW. Scintigraphic detection of gastric and pancreatic carcinomas with In-111 ZCE 025 monoclonal antibody. *World J Surg.* 1991 15(1):122-127.

17. Nemunaitis J, Buckner CD, Appelbaum FR, Higano CS, Mori M, Bianco J, Epstein C, Lipani J, Hansen J, Storb R, et al. Phase I/II trial of recombinant human granulocyte-macrophage colony-stimulating factor following allogeneic bone marrow transplantation. *Blood.* 1991 77(9):2065-2071.

18. Higano CS, Crowley J, Livingston RB, Goodwin JW, Barlogie B, Stuckey WJ. A weekly cisplatin-based induction regimen for extensive non-small cell lung cancer. A Southwest Oncology Group study. *Cancer.* 1991 67(10):2439-2442.

19. Nemunaitis J, Meyers JD, Buckner CD, Shannon-Dorcy K, Mori M, Shulman H, Bianco JA, Higano CS, Groves E, Storb R, Hansen J, Appelbaum FR, Singer JW. Phase I trial of recombinant human macrophage colony-stimulating factor in patients with invasive fungal infections. *Blood.* 1991 78(4):907-913.

20. Higano CS, Goodman P, Craig JB, Kish JA, Rivkin SE, Wolf M, Crawford ED. Phase II evaluation of amonafide in renal cell carcinoma. A Southwest Oncology Group study. *Invest New Drugs.* 1991 9(4):361-363.

21. Department of Veterans Affairs Laryngeal Cancer Study Group. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. *N Engl J Med* 1991 324:1685-1690.

22. Case DC Jr, Gerber MC, Gams RA, Crawford J, Votaw ML, Higano CS, Pruitt BT, Gould J. Phase II study of intravenous idarubicin in unfavorable non-Hodgkin's lymphoma. *Cancer Res.* 1992 52(14):3871-3874.

23. Hommeyer SC, Teefey SA, Jacobson AF, Higano CS, Bianco JA, Colacurcio CJ, McDonald GB. Venoocclusive disease of the liver: prospective study of US evaluation. *Radiology.* 1992 184(3):683-686.

24. Higano CS, Raskind WH, Singer JW. Use of alpha interferon for treatment of relapse of chronic myelogenous leukemia in chronic phase after allogeneic bone marrow transplantation. *Blood.* 1992 80(6):1437-1442.

25. Higano CS, Raskind WH, Singer JW. Use of interferon alfa-2a to treat hematologic relapse of chronic myelogenous leukemia after bone marrow transplantation. *Acta Haematol.* 1993;89 Suppl 1:8-14.

26. Wolf GT, Fisher SG, Department of Veterans Affairs Laryngeal Cancer Study Group. Effectiveness of salvage neck dissection for advanced regional metastases when induction chemotherapy and radiation are used for organ preservation. *Laryngoscope.* 1992 102:934-939.

27. Case DC Jr, Gerber MC, Gams RA, Crawford J, Votaw ML, Higano CS, Pruitt BT, Gould J. Phase II study of intravenous idarubicin in unfavorable non-Hodgkin's lymphoma. *Leuk Lymphoma.* 1993 10 Suppl:73-79.

28. Jacobson AF, Teefey SA, Lee SP, Hollister MS, Higano CS, Bianco JA. Frequent occurrence of new hepatobiliary abnormalities after bone marrow transplantation: results of a prospective study using scintigraphy and sonography. *Am J Gastroenterol.* 1993 88(7):1044-1049.

29. Jacobson AF, Teefey SA, Higano CS, Bianco JA. Increased lung uptake of 99Tcm-sulfur colloid as an early indicator of the development of hepatic veno-occlusive disease in bone marrow transplant patients. *Nucl Med Commun.* 1993 14(8):706-711.

30. Teefey SA, Hollister MS, Lee SP, Jacobsen AF, Higano CS, Bianco JA, Colacurcio CJ. Gallbladder sludge formation after bone marrow transplant: sonographic observations. *Abdom Imaging.* 1994 19(1):57-60.

31. Applebaum FR, Clift R, Buckner CD, Anasetti C, Radich J, Higano T, Storb R, Hansen J, Thomas ED. Allogeneic marrow transplantation for chronic myeloid leukemia. *Med Oncol.* 1994; 11(2):69-74. Review.

32. Bensinger WI, Longin K, Appelbaum F, Rowley S, Weaver C, Lilleby K, Gooley T, Lynch M, Higano T, Klarnet J, et al. *Br J Haematol.* 1994 Aug;87(4):825-31.

33. Higano CS, Ellis WJ, Russell K, Lange PH. Intermittent androgen suppression with leuprolide and flutamide for prostate cancer: a pilot study. *Urology.* 1996 48(5):800-804.

34. Higano CS, Crowley JJ, Veith RV, Livingston RB. A phase II trial of intravenous vinorelbine in previously untreated patients with extensive small cell lung cancer, a Southwest Oncology Group study. *Invest New Drugs.* 1997 15(2):153-156.

35. Higano CS, Chielens D, Raskind W, Bryant E, Flowers ME, Radich J, Clift R, Appelbaum FR. Use of alfa-2a-interferon to treat cytogenetic relapse of chronic myeloid leukemia after marrow transplantation. *Blood.* 1997 90(7):2549-2554.

36. Higano CS. Response (to Letter to the Editor). *Blood* 1998 91:2618.

37. Liu AY, True LD, LaTray L, Ellis WJ, Vessella RL, Lange PH, Higano CS, Hood L, van den Engh G. Analysis and sorting of prostate cancer cell types by flow cytometry. *Prostate.* 1999 40(3):192-199.

38. Flowers ME, Leisenring W, Beach K, Riddell S, Radich JP, Higano CS, Rowley SD, Chauncey TR, Sanders JE, Anasetti C, Storb R, Wade J, Appelbaum FR, Martin P. Granulocyte colony-stimulating factor given to donors before apheresis does not prevent aplasia in patients treated with donor leukocyte infusion for recurrent chronic myeloid leukemia after bone marrow transplantation. *Biol Blood Marrow Transplant.* 2000 6(3A):321-326.

39. Deck AJ, True LD and Higano CS. Tricuspid valve metastasis from testicular carcinoma: a case report and review of the literature. *Urology.* 2000 56(2):330.

40. McNeel DG, Ngyuen LD, Ellis WJ, Higano CS, Lange PH, Disis ML. Naturally occurring prostate cancer antigen-specific T cell responses of a Th1 phenotype can be detected in patients with prostate cancer. *Prostate* 2001 47(3):222-229.

41. Corey E, Brown LG, Quinn JE, Poot M, Roudier MP, Higano CS, Vessella RL. Zoledronic acid exhibits inhibitory effects on osteoblastic and osteolytic metastases of prostate cancer. *Clin Cancer Res.* 2003 9(1):295-306.

42. Pfitzenmaier J, Vessella RL, Higano CS, Noteboom JL, Wallace D Jr, Corey E. Elevation of cytokine levels in cachectic patients with prostate cancer. *Cancer.* 2003 97(5):1211-1216.

43. Higano CS. Side effects of androgen deprivation therapy: monitoring and minimizing toxicity. *Urology* 2003 Feb;61(2 Suppl 1):32-38 Review.

44. Wang Z, Corey E, Hass GM, Higano CS, True LD, Wallace D Jr, Tisdale MJ, Vessella RL. Expression of the human cachexia-associated protein (HCAP) in prostate cancer and in a prostate cancer animal model of cachexia. *Intl J Cancer.* 2003 105(1):123-129.

45. Roudier MP, Vesselle H, True LD, Higano CS, Ott SM, King SH, Vessella RL. Bone histology at autopsy and matched bone scintigraphy findings in patients with hormone refractory prostate cancer: the effect of bisphosphonate therapy on bone scintigraphy results. *Clin Exp Metastasis.* 2003 20(2):171-180.

46. Roudier MP, True LD, Higano CS, Vesselle H, Ellis WJ, Lange PH, Vessella RL. Phenotypic heterogeneity of end-stage prostate carcinoma metastatic to bone. *Hum Pathol.* 2003 34(7):646-653.

47. Cherrier MM, Rose AL, Higano CS. The effects of combined androgen blockade on cognitive function during the first cycle of intermittent androgen suppression in patients with prostate cancer. *J Urol.* 2003 170(5):1808-1811.

48. Carroll PR, Benaron DA, Blackledge G, Coakley FV, D'Amico AV, Higano CS, Iversen P, Kattan M, Nanus DM, Nelson JB, Oh WK, Roach M 3rd, Sellers WR, Smith MR, McMann MC, Kantoff PW. Third international conference on innovations and challenges in prostate cancer: prevention, detection and treatment. *J Urol.* 2003 Dec;170(6 Pt 2):S3-5. Review.

49. Higano CS. Management of bone loss in men with prostate cancer. *J. Urol.* 2003 Dec ; 170(6 Pt 2) :S59-63. Review.

50. Scher HI, Eisenberger M, D'Amico AV, Halabi S, Small EJ, Morris M, Kattan MW, Roach M, Kantoff P, Pienta KJ, Carducci MA, Agus D, Slovin SF, Heller G, Kelly WK, Lange PH, Petrylak D, Berg W, Higano CS, Wilding G, Moul JW, Partin AN, Logothetis C, Soule HR. Eligibility and outcomes reporting guidelines for clinical trials for patients in the state of a rising prostate-specific antigen: recommendations from the Prostate-Specific Antigen Working Group. *J Clin Oncol.* 2004 22(3):537-556.

51. Higano CS, Vogelzang NJ, Sosman JA, Feng A, Caron D, Small EJ. Safety and biological activity of repeated doses of recombinant human Flt3 ligand in patients with bone scan-negative hormone-refractory prostate cancer. *Clin Cancer Res.* 2004 Feb 15;10(4):1219-1225.

52. Beer TM, Garzotto M, Lowe BA, Ellis WJ, Montalto MA, Lange PH, Higano CS. Phase I study of weekly mitoxantrone and docetaxel before prostatectomy in patients with high-risk localized prostate cancer. *Clin Cancer Res.* 2004 Feb 15;10(4):1306-1311.

53. Diamond TH, Higano CS, Smith MR, Guise TA, Singer FR. Osteoporosis in men with prostate carcinoma receiving androgen-deprivation therapy: recommendations for diagnosis and therapies. *Cancer.* 2004 100(5):892-899.

54. Roudier MP, True LD, Vessella RL, Higano CS. Metastatic conventional prostatic andeocarcinoma with diffuse chromogranin A and androgren receptor positivity. *J Clin Pathol.* 2004 57(3):321-323.

55. Higano C. Androgen-deprivation therapy for prostate cancer. *Clin Prostate Cancer.* 2004 Jun;2(1):22-23.

56. Higano CS. Understanding treatments for bone loss and bone metastases in patients with prostate cancer: a practical review and guide for the clinician. *Urol Clin North Am.* 2004 31(2):331-352.

57. Lai JS, Brown LG, True LD, Hawley SJ, Etzioni RB, Higano CS, Ho SM, Vessella RL, Corey E. Metastases of prostate cancer express estrogen receptor-beta. *Urology.* 2004 64(4):814-820.

58. Chang SS, Benson MC, Campbell SC, Crook J, Dreicer R, Evans CP, Hall MC, Higano CS, Kelly WK, Sartor O, Smith JA Jr, Society of Urologic Oncology, Shaumberg, Illinois. Society of Urologic Oncology position statement: redefining the management of hormone-refractory prostate carcinoma. *Cancer.* 2005 103(1):11-21.

59. Higano CS, Shields A, Wood N, Brown J, Tangen C. Bone mineral density in patients with prostate cancer without bone metastases treated with intermittent androgen suppression. *Urology.* 2004 64(6):1182-1186.

60. Gulley JL, Figg WD, Steinberg SM, Carter J, Sartor O, Higano CS, Petrylak DP, Chatta G, Hussain MH, Dahut WL. A prospective analysis of the time to normalization of serum androgens following 6 months of androgen deprivation therapy in patients on a randomized phase III clinical trial using limited hormonal therapy. *J Urol.* 2005 173(5):1567-1571. Erratum in *J Urol.* 2005 174(2):796.

61. Smith MR, Kabbinavar F, Saad F, Hussain A, Gittelman MC, Bilhartz DL, Wynne C, Murray R, Zinner NR, Schulman C, Linnartz R, Zheng M, Goessl C, Hei Y-J, Small EJ, Cook R, Higano CS. Natural history of rising serum prostate-specific antigen in men with castrate nonmetastatic prostate cancer. *J Clin Oncol.* 2005 23(13):2918-2925.

62. Higano CS. Current status of treatment for patients with metastatic prostate cancer. *Can J Urol.* 2005 Jun;12 Suppl 2:38-41. Review.

63. Wright JL, Higano CS, Lin DW. Intermittent androgen deprivation: clinical experience and practical applications. *Urol Clin North Am.* 2006 May;33(2):167-179. Review.

64. Garzotto M, Myrthue A, Higano CS, Beer TM. Neoadjuvant mitoxantrone and docetaxel for high-risk localized prostate cancer. *Urol Oncol.* 2006 24(3):254-259.

65. Saad F, Higano CS, Sartor O, Colombel M, Murray R, Mason MD, Tubaro A, Schulman C. The role of bisphosphonates in the treatment of prostate cancer: recommendations from an expert panel. *Clin Genitourin Cancer.* 2006 4(4):257-262.

66. Small EJ, Schellhammer PF, Higano CS, Redfern CH, Nemunaitis JJ, Valone, FH, Verjee SS, Jones LA, Hershberg RM. Placebo-controlled phase III trial of immunologic therapy with sipuleucel-T (APC8015) in patients with metastatic asymptomatic hormone refractory prostate cancer. *J Clin Oncol.* 2006 24(19):3089-3094.

67. Higano C. Androgen deprivation therapy: monitoring and managing the complications. *Hematol Oncol Clin North Am.* 2006 Aug;20(4):909-923. Review.

68. Hussain M, Tangen C, Higano C, Schellhammer PF, Faulkner J, Crawford ED, Wilding G, Akdas A, Small E, Donnelly B, MacVicar G, Raghavan D; Southwest Oncology Group Trial 9346 (INT-0162). Absolute prostate-specific antigen value after androgen deprivation is a strong independent predictor of survival in new metastatic prostate cancer: data from Southwest Oncology Group Trial 9346 (INT-0162). *J Clin Oncol.* 2006 24(24):3984-3990.

69. Cookson MS, Aus G, Burnett AL, Canby-Hagino ED, D'Amico AV, Dmochowski RR, Eton DT, Forman JD, Goldenberg SL, Hernandez J, Higano CS, Kraus SR, Moul JW, Tangen C, Thrasher JB, Thompson I. Variation in the definition of

biochemical recurrence in patients treated for localized prostate cancer: the American Urological Association Prostate Guidelines for Localized Prostate Cancer Update Panel report and recommendations for a standard in the reporting of surgical outcomes. *J Urol.* 2007 Feb;177(2):540-5. Review. *Prac Rad Onc.* 2014: 4(6): 409-414. *European J Can.* 2015: 51(5): 604-609. *Reports of Prac Onc Rad.* 2015: 20(2): 113-122.

70. Beer TM, Ryan CW, Venner PM, Petrylak DP, Chatta G, Ruether D, Redfern CH, Fehrenbacher L, Saleh MN, Waterhouse D, Carducci MA, Bicario D, Dreicer R, Higano CS, Ahmann FR, Chi KN, Henner WD, Arroyo A, Clow FW, ASCENT investigators. Double-blinded randomized study of high-dose calcitriol plus docetaxel compared with placebo plus docetaxel in androgen-independent prostate cancer: a report from the ASCENT Investigators. *J Clin Oncol.* 2007 25(6):669-674.

71. Higano CS. Annual zoledronic acid: is less more? *J Clin Oncol.* 2007 Mar 20;25(9):1026.

72. Thompson I, Thrasher J, Brantley J, Aus G, Burnett AL, Canby-Hagino ED, Cookson MS, D'Amico AV, Domochowski RR, Eaton DT, Forman JD, Goldenberg SL, Hernandez J, Higano CS, Kraus SR, Moul JW, Tangen CM; Prostate Cancer Clinical Guideline Update Panel. Guideline for the management of clinically localized prostate cancer: 2007 update. *J Urol.* 2007 177(6):2106-2131. *Brachytherapy.* 2015 14(2): 166-172.

73. Burnett AL, Aus G, Canby-Hagino ED, Cookson MS, D'Amico AV, Dmochowski RR, Eton DT, Forman JD, Goldenberg SL, Hernandez J, Higano CS, Kraus S, Liebert M, Moul JW, Tangen C, Thrasher JB, Thompson I; American Urological Association Prostate Cancer Guideline Update Panel. Erectile function outcome reporting after clinically localized prostate cancer treatment. *J Urol.* 2007 Aug;178(2):597-601. Epub 2007 Jun 13. Review.

74. Beer TM, Higano CS, Saleh M, Dreicer R, Hudes G, Picus J, Rarick M, Fehrenbacher L. Phase II Study of KOS-862 in patients with metastatic androgen independent prostate cancer previously treated with docetaxel. *Invest New Drugs.* 2007 25(6):565-570.

75. Beer TM, Bergenstock, Birt K, Higano CS. Darbepoetin alfa administered every 4 weeks for anemia in advanced prostate cancer patients. *Clin Genitourin Cancer.* 2007 5(5):329-333.

76. Gross M, Higano C, Pantuck A, Castellanos O, Green E, Nguyen K, Agus DB. A phase II trial of docetaxel and erlotinib as first-line therapy for elderly patients with androgen-independent prostate cancer. *BMC Cancer.* 2007 7(1):142.

77. Huang CY, Beer TM, Higano CS, True LD, Vessella R, Lange PH, Garzotto M, Nelson PS. Molecular alterations in prostate carcinomas that associate with in vivo exposure to chemotherapy: identification of a cytoprotective mechanism involving growth differentiation factor15. *Clin Cancer Res* 2007 13(19):5825-5833.

78. Basch EM, Somerfield MR, Beer TM, Carducci MA, Higano CS, Hussain MH, Scher HI; American Society of Clinical Oncology. American Society of Clinical Oncology endorsement of the Cancer Care Ontario Practice Guideline on nonhormonal therapy for men with metastatic hormone-refractory (castration-resistant) prostate cancer. *J Clin Oncol.* 2007 Nov 20;25(33):5313-8. Epub 2007 Oct 9. Review.

79. Morrissey C, True LD, Roudier MP, Coleman IM, Hawley S, Nelson PS, Coleman R, Wang YC, Corey E, Lange PH, Higano CS, Vessella RL. Differential expression of angiogenesis associated genes in prostate cancer bone, liver and lymph node metastases. *Clin Exp Metastasis* 2007 25(4):377-388.

80. Higano CS. Androgen-deprivation-therapy-induced fractures in men with nonmetastatic prostate cancer: what do we really know? *Nat Clin Pract Urol.* 2008 Jan;5(1):24-34. Review.

81. Guise TA, Oefelein MG, Eastham JA, Cookson MS, Higano CS, Smith MR. Estrogenic side effects of androgen deprivation therapy. *Rev Urol* 2007 Fall;9(4):163-180.

82. Scher HI, Halabi S, Tannock I, Morris M, Sternberg C, Carducci M, Eisenberger MA, Higano CS, Bubley GJ, Dreicer R, Petyrlak D, Kantoff P, Heller G, Basch E, Kelly WK, Figg WD, Small EJ, Beer TM, Wilding G, Martin A, Hussain M. Design and endpoints of Phase 2 trials for patients with progressive prostate cancer and castrate levels of testosterone. Recommendation of the Prostate Cancer Trials Working Group (PCWG2). *J Clin Oncol* 2008 26(7):1148-1159.

83. Higano CS, Tangen CM, Sakr WA, Faulkner J, Rivkin SE, Gandara DR, Hussain M, Baker LH, Russell KJ, Raghavan D, Crawford ED; Southwest Oncology Group Trial 8733. Treatment options for muscle invasive urothelial cancer for patients who were not eligible for cystectomy or neoadjuvant chemotherapy with methotrexate, vinblastine, adriamycin, and cisplatin: report of Southwest Oncology Group Trial 8733. *Cancer* 2008 112(10):2181-2187.

84. Higano CS, Quick DP, Bushnell D, Sartor O. Safety analysis of repeated high doses of samarium-153 lexidronam in men with hormone-naïve prostate cancer metastatic to bone. *Clin Genitourin Cancer* 2008 6(1):40-45.

85. Montgomery RB, Mostaghel EA, Vessella R, Hess DL, Kalhorn TF, Higano CS, True LD, Nelson PS. Maintenance of intratumoral androgens in metastatic prostate cancer: a mechanism for castration-resistant tumor growth. *Cancer Res* 2008 68(11):4447-4454.

86. Cherrier MM, Aubin S, Higano CS. Cognitive and mood changes in men undergoing intermittent combined androgen blockade for non-metastatic prostate cancer. *Psychooncology* 2009 18(3):237-247.

87. Roudier MP, Morrissey C, True LD, Higano CS, Vessella RL, Ott SM. Histopathologic assessment of prostate cancer bone "osteoblastic" metastasis. *J Urol* 2008 180(3):1154-1160.

88. Higano CS, Corman JM, Smith DC, Centeno AS, Steidle CP, Gittleman M, Simons JW, Sacks N, Aimi J, Small EJ. Phase 1/2 dose-escalation study of GM-CSF-secreting, allogeneic cellular immunotherapy for metastatic hormone-refractory prostate cancer. *Cancer* 2008 113(5):975-984.

89. Gulley JL, Aragon-Ching JB, Steinberg SM, Hussain MH, Sartor O, Higano CS, Petrylak DP, Chatta GS, Arlen PM, Figg WD, Dahut WL. Kinetics of serum androgen normalization and factors associated with testosterone reserve after limited androgen deprivation therapy for nonmetastatic prostate cancer. *J Urol.* 2008 Oct;180(4):1432-1437.

90. Hussain A, DiPaola RS, Baron AD, Higano CS, Tchekmedyian NS, Johri AR. Phase II trial of weekly patupilone in patients with hormone-refractory prostate cancer. *Ann Oncol* 2009 Mar;20(3):492-497.

91. Higano CS. Positive surgical margins: the argument for androgen deprivation and chemotherapy. *Urol Oncol.* 2009 Jan-Feb;27(1):89-91 Review.

92. Dorff TB, Tangen CM, Crawford ED, Petrylak DP, Higano CS, Raghavan D, Quinn DI, Vogelzang NJ, Thompson IM, Hussain MHA. Cooperative group trials – Southwest Oncology Group (SWOG) innovations in advanced prostate cancer. *Ther Adv Med Oncol.* 2009;1(2):69-77.

93. Zerbib M, Zelefsky MJ, Higano CS, Carroll PR. Conventional treatments of localized prostate cancer. *Urology.* 2008 Dec;72(6 Suppl):S25-535.

94. Sunami E, Shinozaki M, Higano CS, Wollman R, Dorff TB, Tucker SJ, Martinez SR, Mizuno R, Singer FR, Hoon D. Multimarker circulating DNA assay for assessing prostate cancer patient's blood. *Clin Chem* 2009 55(3):559-567.

95. Figg WD, Hussain MH, Gulley JL, Arlen PM, Aragon-Ching JB, Petrylak DP, Higano CS, Steinberg SM, Chatta GS, Parnes H, Wright JJ, Sartor O, Dahut WL. A double blind randomized crossover study of oral thalidomide versus placebo in patients with androgen dependent prostate cancer treated by intermittent androgen ablation. *J Urol* 2009 181(3):1104-1113.

96. Morris MJ, Basch EM, Wilding G, Hussain M, Carducci MA, Higano C, Kantoff P, Oh WK, Small EJ, George D, Mathew P, Beer TM, Slovin SF, Ryan C, Logothetis C, Scher HI. Department of Defense prostate cancer clinical trial consortium: a new instrument for prostate cancer clinical research. *Clin Genitourin Cancer* 2009 7(1):51-57.

97. Tran C, Ouk S, Clegg NJ, Chen Y, Watson PA, Arora V, Wongvipat J, Smith-Jones PM, Yoo D, Kwon A, Wasielewska T, Welsbie D, Chen C, Higano CS, Beer TM, Hung DT, Scher HI, Jung M, Sawyers CL. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. *Science* 2009 324(5928):787-790.

98. Qian DZ, Huang CY, O'Brien CA, Coleman IM, Garzotto M, True LD, Higano CS, Vessella R, Lange PH, Nelson PS, Beer TM. Prostate cancer-associated gene expression alterations determined from needle biopsies. *Clin Cancer Res* 2009 15(9):3135-3142.

99. Dean JP, Higano CS. Does chemotherapy have a role before hormone-resistant disease develops? *Curr Urol Rep.* 2009 10(3):226-235.

100. Hussain M, Goldman B, Tangen C, Higano CS, Petrylak DP, Wilding G, Akdas AM, Small EJ, Donnelly BJ, Collette L, Burch PA, DiPaola RS, Crawford ED. Prostate-specific antigen progression predicts overall survival in patients with metastatic prostate cancer: data from Southwest Oncology Group Trials 9346 and 9916. *J Clin Oncol* 2009 27(15):2450-2456.

101. Higano CS, Schellhammer PF, Small EJ, Burch PA, Nemunaitis JJ, Yuh L, Provost N, Frohlich MW. Integrated data from 2 randomized, double-blind, placebo-controlled, phase 3 trials of active cellular immunotherapy with sipuleucel-T in advanced prostate cancer. *Cancer* 2009 115(16):3670-3679.

102. Lord JD, Hackman RC, Moklebust A, Thompson JA, Higano CS, Chielens D, Steinbach G, McDonald GB. Refractory colitis following anti-CTLA4 antibody therapy: analysis of mucosal POXP3+ T cells. *Dig Dis Sci.* 2010 May;55(5):1396-405.

103. Sartor O, McLeod DG, Halabi S, Schellhammer PF, Scardino PT, D'Amico AV, Bennett C, Wei JT; COMPARE Registry Steering Committee. The COMPARE Registry: design and baseline patterns of care for men with biochemical failure after definitive treatment of localized prostate cancer. *Urology*. 2010 Mar;75(3):623-629.

104. Molife LR, Attard G, Fong PC, Karavasilis V, Reid AH, Patterson S, Riggs CE Jr, Higano C, Stadler WM, McCulloch W, Dearnaley D, Parker C, de Bono JS. Phase II, two-stage, single-arm trial of the histone deacetylase inhibitor (HDACi) romidepsin in metastatic castration-resistant prostate cancer (CRPC). *Ann Oncol.* 2010 Jan;21(1):109-113.

105. Holcomb IN, Young JM, Coleman L, Salari K, Grove DI, Hsu L, True LD, Roudier MP, Morrissey CM, Higano CS, Nelson PS, Vessella RL, Trask BJ. Comparative analyses of chromosome alterations in soft-tissue metastates within and across patients with castration-resistant prostate cancer. *Cancer Res* 2009 69(19):7793-7802.

106. Qian DZ, Rademacher BL, Pittsenbarger J, Huang CY, Myrthue A, Higano CS, Garzotto M, Nelson PS, Beer TM. CCL2 is induced by chemotherapy and protects prostate cancer cells from docetaxel-induced cytotoxicity. *Prostate*. 2010 Mar 1;70(4):433-442.

107. Cherrier MM, Borghesani PR, Shelton AL, Higano CS. Changes in neuronal activation patterns in response to androgen deprivation therapy: A Pilot study. *BMC Cancer* 2010 Jan 4;10:1.

108. Garzotto M, Higano CS, O'Brien C, Rademacher BL, Janeba N, Fazli L, Lange PH, Lieberman S, Beer TM. Phase 1/2 study of preoperative docetaxel and mitoxantrone for high-risk prostate cancer. *Cancer.* 2010 Apr;116(7):1699-1708.

109. O'Brien C, True LD, Higano CS, Rademacher BL, Garzotto M, Beer TM. Histologic changes associated with neoadjuvant chemotherapy are predictive of nodal metastases in patients with high-risk prostate cancer. *Am J Clin Pathol.* 2010 Apr;133(4):654-661.

110. Scher HI, Beer TM, Higano CS, Anand A, Taplin ME, Efstathiou E, Rathkopf D, Shelkey J, Yu EY, Alumkal J, Hung D, Hirmand M, Seely L, Morris MJ, Danila DC, Humm J, Larson S, Fleisher M, Sawyers CL; Prostate Cancer Foundation/Department of Defense Prostate Cancer Clinical Trials Consortium. Antitumour activity of MDV3100 in castration-resistant prostate cancer: a phase 1-2 study. Lancet. 2010 Apr 24;375(9724):1437-1446. doi: 10.1016/S0140-6736(10)60172-9. Epub 2010 Apr 14.

111. Yu EY, Gulati R, Telesca D, Jiang P, Tam S, Russell KJ, Nelson PS, Etzioni RD, Higano CS. Duration of First Off-Treatment Interval Is Prognostic for Time to Castration Resistance and Death in Men With Biochemical Relapse of Prostate Cancer Treated on a Prospective Trial of Intermittent Androgen Deprivation. J Clin Oncol 2010; 28(16):2668-2673.

112. Higano CS, Small EJ, Schellhammer P, Yasothan U, Gubernick S, Kirkpatrick P, Kantoff PW: Sipuleucel-T. *Nat Rev Drug Discov.* 2010 July;9(7):513-514.

113. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, Redfern CH, Ferrari AC, Dreicer R, Sims RB, Xu Y, Frohlich MW, Schellhammer PF; IMPACT Study Investigators. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med.* 2010 Jul 29;363(5):411-422; *Reviews on Cancer* vol 1846 issue 2, year 2014, pp.560-575.

114. Scher HI, Beer TM, Higano CS, et al. Prostate Cancer Foundation/Department of Defense Prostate Cancer Clinical Trials Consortium. Words of wisdom. Re: Antitumour activity of MDV3100 in castration-resistant prostate cancer: a phase 1-2 study. *Eur Urol.* 2010 Sep;58(3):464-465.

115. International Prognostic Factors Study Group, Lorch A, Beyer J, Bascoul-Mollevi C, Kramar A, Einhorn LH, Necchi A, Massard C, De Giorgi U, Fléchon A, Margolin KA, Lotz JP, Germa Lluch JR, Powles T, Kollmannsberger CK. Prognostic factors in patients with metastatic germ cell tumors who experienced treatment failure with cisplatin-based first-line chemotherapy. *J Clin Oncol.* 2010 Nov 20;28(33):4906-4911.

116. Yu EY, Muzi M, Hackenbracht JA, Rezvani BB, Link JM, Montgomery RB, Higano CS, Eary JF, Mankoff DA. C11-acetate and F-18 FDG PET for men with prostate cancer bone metastases: relative findings and response to therapy. *Clin Nucl Med*. 2011 Mar;36(3):192-198.

117. Cheever MA, Higano CS. PROVENGE (Sipuleucel-T) in prostate cancer: the first FDA-approved therapeutic cancer vaccine. *Clin Cancer Res*. 2011 Jun 1;17(11):3520-3526.

118. Lorch A, Bascoul-Mollevi C, Kramar A, Einhorn L, Necchi A, Massard C, De Giorgi U, Flechon A, Margolin K, Lotz JP, Germa-Lluch JR, Powles T, Kollmannsberger C, Beyer J. Acknowledged contributing center Higano CS. Conventional-dose versus high-dose chemotherapy as first salvage treatment in male patients with metastatic germ cell tumors: evidence from a large international database. *J Clin Oncol*. 2011 June 1;29(16):2178-2184.

119. Higano CS. New treatment options for patients with metastatic castration-resistant prostate cancer. *Cancer Treat Rev*. 2012 Aug;38(5):340-345.

120. Schwartzman J, Mongoue-Tchokote S, Gibbs A, Gao L, Corless CL, Jin J, Zarour L, Higano C, True LD, Vessella RL, Wilmot B, Bottomly D, McWeeney SK, Bova GS, Partin AW, Mori M, Alumkal J. A DNA methylation microarray-based study identifies ERG as a gene commonly methylated in prostate cancer. *Epigenetics*. 2011 Oct 1;6(10):1248-1256.

121. Sonpavde G, Di Lorenzo G, Higano CS, Kantoff PW, Madan R, Shore ND. The role of sipuleucel-T in therapy for castration-resistant prostate cancer: a critical analysis of the literature. *Eur Urol*. 2012 Apr;61(4):639-647.

122. Yu EY, Kuo KF, Gulati R, Chen S, Gambol TE, Hall SP, Jiang PY, Pitzel P, Higano CS. Long-term dynamics of bone mineral density during intermittent androgen deprivation for men with nonmetastatic, hormone-sensitive prostate cancer. *J Clin Oncol*. 2012 May 20;30(15):1864-1870.

123. Hirata Y, Akakura K, Higano CS, Bruchovsky N, Aihara K. Quantitative mathematical modeling of PSA dynamics of prostate cancer patients treated with intermittent androgen suppression. *J Mol Cell Biol*. 2012 Jun;4(3):127-132.

124. Yu EY, Miller K, Nelson J, Gleave M, Fizazi K, Moul JW, Nathan FE, Higano CS. Detection of previously unidentified metastatic disease as a leading cause of screening failure in a phase III trial of zibotentan versus placebo in patients with nonmetastatic, castration resistant prostate cancer. *J Urol*. 2012 Jul;188(1):103-109.

125. Nelson JB, Fizazi K, Miller K, Higano C, Moul JW, Akaza H, Morris T, McIntosh S, Pemberton K, Gleave M. Phase 3, randomized, placebo-controlled study of zibotentan (ZD4054) in patients with castration-resistant prostate cancer metastatic to bone. *Cancer*. 2012 Nov 15;118(22):5709-5718.

126. Kantoff PW, Higano CS, Small EJ, Whitmore JB, Frohlich MW, Schellhammer PF. Re: interdisciplinary critique of sipuleucel-T as immunotherapy in castration-resistant prostate cancer. *J Natl Cancer Inst*. 2012 Jul 18;104(14):1107-1109.

127. Sun Y, Campisi J, Higano C, Beer TM, Porter P, Coleman I, True L, Nelson PS. Treatment-induced damage to the tumor microenvironment promotes prostate cancer therapy resistance through WNT16B. *Nat Med*. 2012. 18:1359–1368.

128. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, de Wit R, Mulders P, Chi KN, Shore ND, Armstrong AJ, Flaig TW, Fléchon A, Mainwaring P, Fleming M, Hainsworth JD, Hirmand M, Selby B, Seely L, de Bono JS; AFFIRM Investigators. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med*. 2012 Sep 27;367(13):1187-1197.

129. Tangen CM, Hussain MH, Higano CS, Eisenberger MA, Small EJ, Wilding G, Donnelly BJ, Schelhammer PF, Crawford ED, Vogelzang NJ, Powell IJ, Thompson IM Jr. Improved Overall Survival Trends of Men with Newly Diagnosed M1 Prostate Cancer: A SWOG Phase III Trial Experience (S8494, S8894 and S9346). *J Urol*. 2012. 188(4):1164-1169.

130. Crook JM, O'Callaghan CJ, Duncan G, Dearnaley DP, Higano CS, Horwitz EM, Frymire E, Malone S, Chin J, Nabid A, Warde P, Corbett T, Angyalfi S, Goldenberg SL, Gospodarowicz MK, Saad F, Logue JP, Hall E, Schellhammer PF, Ding K, Klotz L. Intermittent androgen suppression for rising PSA level after radiotherapy. *N Engl J Med*. 2012 Sep 6;367(10):895-903.

131. Mohler JL, Armstrong AJ, Bahnson RR, Boston B, Busby JE, D'Amico AV, Eastham JA, Enke CA, Farrington T, Higano CS, Horwitz EM, Kantoff PW, Kawachi MH, Kuettel M, Lee RJ, Macvicar GR, Malcolm AW, Miller D, Plimack ER, Pow-Sang JM, Roach M 3rd, Rohren E, Rosenfeld S, Srinivas S, Strope SA, Tward J, Twardowski P, Walsh PC, Ho M, Shead DA.

Prostate Cancer, Version 3.2012 Featured Updates to the NCCN Guidelines. *J Natl Compr Canc Netw*. 2012 Sep 1;10(9):1081-1087.

132. Quinn DI, Shore N, Beer T, Higano CS, Vaishampayan U, Lin D. Sequencing therapy in advanced prostate cancer: focus on sipuleucel-T. *Expert Rev Anticancer Ther.* 2013 Jan;14(1):51-61.

133. Ryan CJ, Smith MR, de Bono JS, Molina A, Logothetis CJ, de Souza P, Fizazi K, Mainwaring P, Piulats JM, Ng S, Carles J, Mulders PF, Basch E, Small EJ, Saad F, Schrijvers D, Van Poppel H, Mukherjee SD, Suttmann H, Gerritsen WR, Flaig TW, George DJ, Yu EY, Efstathiou E, Pantuck A, Winquist E, Higano CS, Taplin ME, Park Y, Kheoh T, Griffin T, Scher HI, Rathkopf DE; COU-AA-302 Investigators. Abiraterone in metastatic prostate cancer without prevous chemotherapy. *N Engl J Med*. 2013 Jan 10;368(2):138-148.

134. Morrissey C, Roudier MP, Dowell A, True LD, Ketchanji M, Welty C, Corey E, Lange PH, Higano CS, Vessella RL. Effects of androgen deprivation therapy and bisphosphonate treatment on bone in patients with metastatic castration resistant prostate cancer: results from the University of Washington rapid autopsy series. *J Bone Miner Res*. 2013 Feb;28(2):333-340.

135. Higano CS. (Special Series: Adult Survivorship) Sexuality and intimacy following definitive treatment and subsequent androgen deprivation therapy for prostate cancer. *J Clin Oncol*. 2012 Oct 20;30(30):3720-5. Erratum in: J Clin Oncol. 2013 Feb 20;31(6):824.

136. Menon MP, Higano CS. Enzalutamide, a Second Generation Androgen Receptor Antagonist: Development and Clinical Applications in Prostate Cancer. *Curr Oncol Rep*. 2013 Apr;15(2):69-75.

137. Fizazi K, Higano C, Nelson J, Gleave M, Miller K, Morris T, Nathan F, McIntosh S, Pemberton K, Moul J. Phase III, randomized, placebo-controlled study of docetaxel in combination with zibotentan (ZD4054) in patients with metastatic castration-resistant prostate cancer. *J Clin Oncol*. 2013 May 10;31(14):1740-1747.

138. Larson SR, Zhang X, Dumpit R, Coleman I, Lakely B, Roudier M, Higano CS, True LD, Lange PH, Montgomery B, Corey E, Nelson PS, Vessella RL, Morrissey C. Characterization of osteoblastic and osteolytic proteins in prostate cancer bone metastases. *Prostate*. 2013 Jun;73(9):932-940.

139. Miller K, Moul JW, Gleave M, Fizazi K, Nelson JB, Morris T, Nathan FE, McIntosh S, Pemberton K, Higano CS. Phase III, randomized, placebo-controlled study of docetaxel in combination with zibotentan (ZD4054) in patients with non-metastatic castration-resistant prostate cancer. *Prostate Cancer Prostatic Dis*. 2013 Jun;16(2):187-192.

140. Higano CS. Potential use of custirsen to treat prostate cancer. *Onco Targets Ther*. 2013 Jun 25;6:785-797.

141. Akfirat C, Zhang X, Ventura A, Berel D, Colangelo ME, Miranti CK, Krajewska M, Reed JC, Higano CS, True LD, Vessella RL, Morrissey C, Knudsen BS. Tumor Cell Survival Mechanisms in Lethal Metastatic Prostate Cancer Differ Between Bone and Soft Tissue Metastases. *J Pathol*. 2013 Jul;230(3):291-297.

142. Slovin SF, Higano CS, Hamid O, Tejwani S, Harzstark A, Alumkal JJ, Scher HI, Chin K, Gagnier P, McHenry MB, Beer TM. Ipilimumab alone or in combination with radiotherapy in metastatic castration-resistant prostate cancer: results from an open-label, multicenter phase I/II study. *Ann Oncol*. 2013 Jul;24(7):1813-1821.

143. Hussain M, Tangen CM, Berry DL, Higano CS, Crawford ED, Liu G, Wilding G, Prescott S, Sundaram SK, Small EJ, Dawson NA, Donnelly BJ, Venner PM, Vaishampayan UN, Schellhammer PF, Quinn DI, Raghavan D, Ely B, Moinpour CM, Vogelzang NJ, and Thompson, IM Jr. Intermittent versus Continuous Androgen Deprivation in Prostate Cancer. *N Engl J Med* 2013; 368(14):1314-1325.

144. Quinn DI, Tangen CM, Hussain M, Lara PN Jr, Goldkorn A, Moinpour CM, Garzotto MG, Mack PC, Carducci MA, Monk JP, Twardowski PW, Van Veldhuizen PJ, Agarwal N, Higano CS, Vogelzang NJ, Thompson IM Jr. Docetaxel and atrasentan versus docetaxel and placebo for men with advanced castration-resistant prostate cancer (SWOG S0421): a randomised phase 3 trial. *Lancet Oncol*. 2013 Aug;14(9):893-900.

145. Qu X, Randhawa G, Friedman C, Kurland B, Glaskova L, Coleman I, Mostaghel E, Higano C, Porter C, Vessella R, Nelson P. A three-marker FISH panel detects more genetic aberrations of AR, PTEN and TMPRSS2/ERG in castration-resistant or metastatic prostate cancers than in primary prostate tumors. *PLoS One*. 2013 Sep 30;8(9):e74671.

146. Cherrier MM, Anderson K, David D, Higano CS, Gray H, Church A, Willis SL. A Randomized Trial of Cognitive Rehabilitation in Cancer Survivors. *Life Sci.* 2013 Oct 17;93(17):617-22.

147. Liu G, Lu S, Wang X, Page ST, Plymate SR, Higano CS, Greenberg NM, Sun S, Li Z, Wu JD. Perturbation of NK cell peripheral homeostasis accelerates prostate carcinoma metastasis. *J Clin Invest.* 2013 Oct 1;123(10):4410-4422.

148. Higano, CS. Urological Cancer: Alpha-emitting radium-223: additional choices, more unknowns. *Nat Rev Clin Oncol.* 2013 Nov;10(11):612-613.

149. Mohler JL; NCCN Prostate Cancer Panel. Joint statement by members of the NCCN Prostate Cancer Guidelines Panel. J Natl Compr Canc Netw. 2013 Nov;11(11):1310-2.

150. Sridhar SS, Freedland SJ, Gleave ME, Higano C, Mulders P, Parker C, Sartor O, Saad F. Castration-Resistant Prostate Cancer: From New Pathophysiology to New Treatment. *Eur Urol.* 2014 Feb;65(2):289-299.

151. Mulders PFA, Molina A, Marberger M, Saad F, Higano CS, Chi KN, Kheoh T, Haqq CM, Fizazi K. Efficacy and Safety of Abiraterone Acetate in Elderly (≥75 Yr) Patient Subgroup with Metastatic Castration-resistant Prostate Cancer Post-Docetaxel-Based Chemotherapy. *Eur Urol.* 2014 May;65(5):875-883.

152. Mohler JL, Kantoff PW, Armstrong AJ, Bahnson RR, Cohen M, D'Amico AV, Eastham JA, Enke CA, Farrington TA, Higano CS, Horwitz EM, Kawachi MH, Kuettel M, Lee RJ, Macvicar GR, Malcolm AW, Miller D, Plimack ER, Pow-Sang JM, Richey S, Roach M 3rd, Rohren E, Rosenfeld S, Small EJ, Srinivas S, Stein C, Strope SA, Tward J, Walsh PC, Shead DA, Ho M. Prostate Cancer, version 1.2014. *J Natl Compr Canc Netw.* 2013 Dec 1; 11(12):1471-1479.

153. Barnett CM, Heinrich MC, Lim J, Nelson D, Beadling C, Higano CS, Thomas G, Warrick A, Neff T, Corless C, Garzotto M, Beer TM. Genetic Profiling to determine Risk of Relapse Free Survival in High Risk Localized Prostate Cancer. *Clin Cancer Res.* 2014 Mar 1;20(5):1306-1312.

154. Higano CS. To Treat or Not to Treat, That is the Question: The Role of Bone-Targeted Therapy in Metastatic Prostate Cancer. *J Clin Oncol.* 2014 Apr 10;32(11):1107-1111.

155. Goldkorn A, Ely B, Quinn DI, Tangen CM, Fink LM, Xu T, Twardowski P, Van Veldhuizen PJ, Agarwal N, Carducci MA, Monk JP 3rd, Datar RH, Garzotto M, Mack PC, Lara P Jr, Higano CS, Hussain M, Thompson IM Jr, Cote RJ, Vogelzang NJ. Circulating Tumor Cell Counts are Prognostic of Overall Survival in SWOG S0421: A Phase III Trial of Docetaxel With or Without Atrasentan for Metastatic Castration-Resistant Prostate Cancer. *J Clin Oncol.* 2014 Apr 10;32(11):1136-1142.

156. Basch EM, Autio KA, Smith MR, Bennett AV, Weitzman AL, Scheffold C, Sweeney C, Rathkopf DE, Smith DC, George DJ, Higano CS, Harzstark AL, Sartor AO, Gordon MS, Vogelzang NJ, de Bono JS, Haas NB, Corn PG, Schimmoller F, Scher HI. Effects of Cabozantinib on Pain and Narcotic Use in Patients with Castration-resistant Prostate Cancer: Results from a Phase 2 Nonrandomized Expansion Cohort. *Eur Urol.* 2014 Feb 20. pii: S0302-2838(14)00132-138.

157. Rathkopf DE, Smith MR, de Bono JS, Logothetis CJ, Shore ND, de Souza P, Fizazi K, Mulders PF, Mainwaring P, Hainsworth JD, Beer TM, North S, Fradet Y, Van Poppel H, Carles J, Flaig TW, Efstathiou E, Yu EY, Higano CS, Taplin ME, Griffin TW, Todd MB, Yu MK, Park YC, Kheoh T, Small EJ, Scher HI, Molina A, Ryan CJ, Saad F. Updated Interim Efficacy Analysis and Long-Term Safety of Abiraterone Acetate in Metastatic Castration-resistant Prostate Cancer Patients without prior Chemotherapy (COU-AA-302). *Eur Urol.* 2014 Mar 6. pii: S0302-2838(14)00185-00187.

158. Mohler JL, Kantoff PW, Armstrong AJ, Bahnson RR, Cohen M, D'Amico AV, Eastham JA, Enke CA, Farrington TA, Higano CS, Horwitz EM, Kane CJ, Kawachi MH, Kuettel M, Kuzel TM, Lee RJ, Malcolm AW, Miller D, Plimack ER, Pow-Sang JM, Raben D, Richey S, Roach M 3rd, Rohren E, Rosenfeld S, Schaeffer E, Small EJ, Sonpavde G, Srinivas S, Stein C, Strope SA, Tward J, Shead DA, Ho M. Prostate cancer, version 2.2014. *J Natl Compr Canc Netw.* 2014 May; 12(5):686-718.

159. Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, Iversen P, Bhattacharya S, Carles J, Chowdhury S, Davis ID, de Bono JS, Evans CP, Fizazi K, Joshua AM, Kim CS, Kimura G, Mainwaring P, Mansbach H, Miller K, Noonberg SB, Perabo F, Phung D, Saad F, Scher HI, Taplin ME, Venner PM, Tombal B; the PREVAIL Investigators. Enzalutamide in Metastatic Prostate Cancer before Chemotherapy. *N Engl J Med.* 2014 Jul 31; 371(5):424-433.

160. Small EJ, Higano CS, Kantoff PW, Whitmore JB, Frohlich MW, Petrylak DP. Time to disease-related pain and first opioid use in patients with metastatic castration-resistant prostate cancer treated with sipuleucel-T. *Prostate Cancer Prostatic Dis.* 2014 Sep;17(3):259-64.

161. Padhi D, Higano CS, Shore N, Sieber P, Rasmissen E, Smith M. Pharmacologic Inhibition of Myostatin and Changes in Lean Body Mass and Lower Extremity Muscle Size in Patients Receiving Androgen Deprivation Therapy for Prostate Cancer. J Clin Endocrinol Metab. 2014 Jun 27:jc20141271. *J Clin Endocrinol Metab*. 2014 Oct;99(10):E1967-1975.

162. Cheng HH, Higano CS. Targeting the androgen receptor signaling axis to reduce testosterone levels in prostate cancer: how low should we go? *Oncology*. 2014 Aug;28(8):700-701.

163. McNeel DG, Gardner TA, Higano CS, Kantoff PW, Small EJ, Wener MH, Sims RB, DeVries T, Sheikh NA, Dreicer R. A transient increase in eosinophils is associated with prolonged survival in men with metastatic castration-resistant prostate cancer who receive sipuleucel-T. *Cancer Immunol Res*. 2014 Oct;2(10):988-999.

164. Gordon RR, Wu M, Huang CY, Harris WP, Sim HG, Lucas JM, Coleman I, Higano CS, Gulati R, True LD, Vessella R, Lange PH, Garzotto M, Beer TM, Nelson PS. Chemotherapy-induced monoamine oxidase expression in prostate carcinoma functions as a cytoprotective resistance enzyme and associates with clinical outcomes. *PLoS One*. 2014 Sep 8;9(9):e104271.

165. Smith MR, Sweeney C, Corn PG, Rathkopf DE, Smith DC, Hussain M, George DJ, Higano CS, Harzstark AL, Sartor AO, Vogelzang NJ, Gordon MS, de Bono JS, Haas NB, Logothetis CJ, Elfiky A, Scheffold C, Laird AD, Schimmoller F, Basch EM, Scher HI. Cabozantinib in chemotherapy-pretreated metastatic castration-resistant prostate cancer: Results of a Phase II non-randomized expansion study. *J Clin Oncol.* 2014 Oct 20;32(30):3391-9. doi: 10.1200/JCO.2013.54.5954. Epub 2014 Sep 15.

166. Chevillet JR, Kang Q, Ruf IK, Briggs HA, Vojtech LN, Hughes SM, Cheng HH, Arroyo JD, Meredith EK, Gallichotte EN, Pogosova-Agadjanyan EL, Morrissey C, Stirewalt DL, Hladik F, Yu EY, Higano CS, Tewari M. Quantitative and stoichiometric analysis of the microRNA content of exosomes. *Proc Natl Acad Sci U S A*. 2014 Oct 14;111(41):14888-14893.

167. Kuo KF Hunter-Merrill R, Gulati R, Hall SP, Gambol TE, Higano CS, Yu EY. Relationships Between Times to Testosterone and Prostate-Specific Antigen Rises During the First Off-Treatment Interval of Intermittent Androgen Deprivation are Prognostic for Castration Resistance in Men With Nonmetastatic Prostate Cancer. *Clin Genitourin Cancer*. 2015 Feb;13(1):10-6.

168. Goldkorn A, Ely B, Tangen CM, Tai YC, Xu T, Li H, Twardowski P, Veldhuizen PJ, Agarwal N, Carducci MA, Monk JP 3rd, Garzotto M, Mack PC, Lara P Jr, Higano CS, Hussain M, Vogelzang NJ, Thompson IM Jr, Cote RJ, Quinn DI. Circulating tumor cell telomerase activity as a prognostic marker for overall survival in SWOG 0421: A phase III metastatic castration resistant prostate cancer trial. *Int J Cancer*. 2015 Apr 15;136(8):1856-62.

169. Mostaghel EA, Morgan A, Zhang X, Marck BT, Xia J, Hunter-Merrill R, Gulati R, Plymate S, Vessella RL, Corey E, Higano CS, Matsumoto AM, Montgomery RB, Nelson PS. Prostate Cancer Characteristics associated with response to pre-receptor targeting of the androgen axis. PLoS One. 2014 Oct 30;9(10):e111545. doi: 10.1371/journal.pone.0111545. eCollection 2014.

170. Klotz L, Nabid A, Higano C, Ryanm C, Kebabdjian M, Chin J. Effect of dutasteride in men receiving intermittent androgen ablation therapy: The AVIAS trial. Can Urol Assoc J. 2014 Nov;8(11-12):E789-94. doi: 10.5489/cuaj.2332.

171. Ryan CJ, Smith MR, Fizazi K, Saad F, Sternberg CN, Miller K, Logothetis CJ, Shore ND, Small EJ, Carles J, Flaig TW, Taplin ME, Higano CS, De Souza P, De Bono JS, Rathkopf. Abiraterone acetate for treatment of chemotherapy-naïve metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-302 randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol*. 2015 Feb; 16(2): 152-60. doi: 10.1016/S1470-2045(14)71205-7. [Epub 2015 Jan 16]. PMID: 25601341.

172. GuhaThakurta D, Sheikh NA, Fan LQ, Kandadi H, Meagher TC, Hall SJ, Kantoff PW, Higano CS, Small EJ, Gardner TA, Bailey K, Vu T, DeVries T, Whitmore JB, Frohlich MW, Trager JB, Drake CG. Humoral Immune Response against non-targeted tumor antigens after treatment with Sipuleucel-T and its association with improved clinical outcome. *Clinc Cancer Res*. 2015 Feb 3. Pii: clincanres.2334.2014. [Epub ahead of print]. doi: 10.1158/1078-0432.CCR-14-2234. PMID: 25649018.

173. Higano CS, Beer TM, Taplin M-E, Efstathiou E, Hirmand M, Forer D, Scher HI. Long-Term Safety and Efficacy Results from the Phase 1–2 Study of Enzalutamide in Pre- and Post-docetaxel Castration-Resistant Prostate Cancer. *Eur Urol*. 2015 Feb 16. Pii: S0302-2838(15)00069-X. doi: 10.1016/j.eururo.2015.01.026. [Epub ahead of print]. PMID: 25698064.

174. Higano CS, Berlin J, Gordon M, LoRusso P, Tang S, Dontabhaktuni A, Schwartz JD, Cosaert J, Mehnert JM. Safety, tolerability, and pharmacokinetics of single and multiple doses of intravenous cixutumumab (IMC-A12), an inhibitor of the insulin-like growth factor-I receptor, administered weekly or every 2 weeks in patients with advanced solid tumors. *Invest New Drugs*. 2015 Apr;33(2):450-62. doi: 10.1007/s10637-015-0217-7. ISSN: 0167-6997. eISSN: 1573-0646. PMID: 25749986.

175. Morris MJ, Molina A, Small EJ, de Bono JS, Logothetis CJ, Fizazi K, de Souza P, Kantoff PW, Higano CS, Li J, Kheoh T, Larson SM, Matheny SL, Naini V, Burzykowski T, Griffin TW, Scher HI, Ryan CJ. Radiographic progression-free survival as a response biomarker in metastatic castration-resistant prostate cancer: COU-AA-302 results. *J Clin Oncol.* 2015 Apr 20;33(12):1356-63. doi: 10.1200/JCO.2014.55.3875. [Epub 2015 Jan 26]. PMID: 25624432.

176. Yu EY, Duan F, Muzi M, Deng X, Chin BB, Alumkal JJ, Taplin ME, Taub JM, Herman B, Higano CS, Doot RK, Hartfeil D, Febbo PG, Mankoff DA. Castration-resistant prostate cancer bone metastasis response measured by 18F-fluoride PET after treatment with dasatinib and correlation with progression-free survival: results from American College of Radiology Imaging Network 6687. *J Nucl Med.* 2015 Mar;56(3):354-60. doi: 10.2967/jnumed.114.146936. [Epub 2015 Jan 29]. PMID: 25635138.

177. Klotz L, O'Callaghan C, Ding K, Toren P, Dearnaley D, Higano CS, Horwitz E, Malone S, Goldenberg L, Gospodarowicz M, Crook JM. Nadir testosterone within first year of androgen-deprivation therapy (ADT) predicts for time to castration-resistant progression: a secondary analysis of the PR-7 trial of intermittent versus continuous ADT. *J Clin Oncol.* 2015 Apr 1;33(10):1151-6. doi: 10.1200/JCO.2014.58.2973. [Epub 2015 Mar 2]. PMID: 25732157.

178. Yu EY, Li H, Higano CS, Agarwal N, Pal SK, Alva A, Heath EI, Lam ET, Gupta S, Lilly MB, Inoue Y, Chi KN, Vogelzang NJ, Quinn DI, Cheng HH, Plymate SR, Hussain M, Tangen CM, Thompson IM Jr. SWOG S0925: A Randomized Phase II Study of Androgen Deprivation Combined With Cixutumumab Versus Androgen Deprivation Alone in Patients With New Metastatic Hormone-Sensitive Prostate Cancer. *J Clin Oncol.* 2015 May 10;33(14):1601-8. doi: 10.1200/JCO.2014.59.4127. [Epub 2015 Apr 6]. PMID: 25847934.

179. Loriot Y, Miller K, Sternberg CN, Fizazi K, De Bono JS, Chowdhury S, Higano CS, Noonberg S, Holmstrom S, Mansbach H, Perabo FG, Phung D, Ivanescu C, Skaltsa K, Beer TM, Tombal B. Effect of enzalutamide on health-related quality of life, pain, and skeletal-related events in asymptomatic and minimally symptomatic, chemotherapy-naïve patients with metastatic castration-resistant prostate cancer (PREVAIL): results from a randomised, phase 3 trial. *Lancet Oncol.* 2015 May;16(5):509-21. doi: 10.1016/S1470-2045(15)70113-0. [Epub 2015 Apr 14]. PMID: 25888263.

180. Aggarwal RR, Beer TM, Weinberg VK, Higano CS, Taplin ME, Ryan CJ, Lin AM, Alumkal J, Graff JN, Nordquist LT, Herrera I, Small EJ. Intermittent Chemotheray as a Platform for Testing Novel Agents in Patients With Metastatic Castration-Resistant Prostate Cancer: A Department of Defense Prostate Cancer Clinical Trials Consortium Randomized Phase II Trial of Intermittent Docetaxel With Prednisone With or Without Maintenance GM-CSF. *Clin Genitourin Cancer.* 2015 June;13(3):e191-8. doi: 10.1016/j.cigc.2014.12.004. [Epub 2014 Dec 9]. PMID: 25557266.

181. Hirata Y, Morino K, Akakura K, Higano CS, Bruchovsky N, Gambol T, Hall S, Tanaka G, Aihara K. Intermittent Androgen Suppression: Estimating Parameters for Individual Patients Based on Initial PSA Data in Response to Androgen Deprivation Therapy. *PLoS One.* 2015 Jun 24;10(6):e0130372. doi: 10.1371/journal.pone.0130372. eCollection 2015. PMID: 26107379.

182. Hussain M, Rathkopf D, Liu G, Armstrong A, Kelly WK, Ferrari A, Hainsworth J, Joshi A, Hozak RR, Yang L, Schwartz JD, Higano CS. A randomised non-comparative phase II trial of cixutumumab (IMC-A12) or ramucirumab (IMC-1121B) plus mitoxantrone and prednisone in men with metastatic docetaxel-pretreated castration-resistant prostate cancer. *Eur J Cancer.* 2015 Sep;51(13):1714-24. doi:10.1016/j.ejca.2015.05.019. [Epub 2015 Jun 13]. PMID: 26082390.

183. Higano CS. The Evolving Role of Immunotherapy in Prostate Cancer. CDMRP PCRPerspectives. Volume 5, Number 1, Sept 2015.

184. Zhang X, Coleman IM, Brown LG, True LD, Kollath L, Lucas JM, Lam HM, Dumpit R, Corey E, Chéry L, Lakely B, Higano CS, Montgomer B, Roudier M, Lange PH, Nelson PS, Vessella RL, Morrissey C. SRRM4 Expression and the Loss of REST Activity May Promote the Emergence of the Neuroendocrine Phenotype in Castration-Resistant Prostate Cancer. *Clin Cancer Res.* 2015 Oct 15;21(20):4698-708. doi: 10.1158/1078-0432. CCR-15-0157. [Epub 2015 June 12]. PMID: 26071481.

185. Higano CS, Beer TM, Taplin ME, Efstathiou E, Hirmand M, Forer D, Scher HI. Long-term Safety and Antitumor Activity in the Phase 1-2 Study of Enzalutamide in Pre- and Post-docetaxel Castration-Resistant Prostate Cancer. *Eur Urol.* 2015 Nov;68(5):795-801. doi: 10.1016/j.eururo.2015.01.026. [Epub 2015 Feb 16]. PMID: 25698064.

186. Crawford ED, Higano CS, Shore ND, Hussain M, Petrylak DP. Treating Patients with Metastatic Castration Resistant Prostate Cancer: A Comprehensive Review of Available Therapies. *J Urol.* 2015 Dec;194(6):1537-47Jul 18. doi: 10.1016/j.juro.2015.06.106. [Epub ahead of print]. Review. PMID: 26196735.

187. Higano CS. Prostate cancer: Mapping the course after CHAARTED. *Nat Rev Urol.* 2015 Dec;12(12):656-8.

188. Crawford ED, Petrylak DP, Higano CS, Kibel AS, Kantoff PW, Small EJ, Shore ND, Ferrari A. Optimal timing of sipuleucel-T treatment in metastatic castration-resistant prostate cancer. *Can J Urol.* 2015 Dec;22(6):8048-55. Review.

189. Graff JN, Thomas GV, Higano CS, Beer TM. Prolonged Response to an IGF-1 Receptor Antibody in a Patient with Metastatic Castration Prostate Cancer with Neuroendocrine Differentiation. *Cureus.* 2015 Dec 22;7(12):e426. doi: 107759/cureus.426. PMID:26848415

190. Hussain M, Tangen C, Higano C, Vogelzang N, Thompson I. Evaluating intermittent androgen-deprivation therapy phase III clinical trials: The devil is in the details. *J Clin Oncol.* 2016 Jan 20;34(3):280-5. Epub 2015 Nov 9.

191. Mohler JL, Armstrong AJ, Bahnson RR, D'Amica AV, Davis BJ, Eastham JA, Enke CA, Farrington TA, Higano CS, Horwitz EM, Jurwitz M, Kane CJ, Kawachi MH, Kuettel M, Lee RJ, Meeks JJ, Penson DF, Plimack ER, Pow-San JM, Raben D, Richey S, Roach M, Rosenfeld S, Schaeffer E, Skolarus TA, Small EJ, Sonpavde G, Srinivas S, Strope SA, Tward J, Shead DA, Freedman-Cass DA. Prostate Cancer, Version 1.2016. *J Natl Compr Canc Netw.* 2016 Jan;14(1):19-30.

192. Graff JN, Baciarello G, Armstrong AJ, Higano CS, Iversen P, Flaig TW, Forer D, Parli T, Phung D, Tombal B, Beer TM, Sternberg CN. Efficacy and safety of enzalutamide in patients 75 hyears or older with chemotherapy-naïve metastatic castration-resistant prostate cancer: results from PREVAIL. *Ann Oncol.* 2016 Feb;27(2):286-94. doi: 10.109/annonc/mdv542. [Epub ahead of print].

193. Haider M, Zhang X, Coleman I, Ericson N, True LD, Lam HM, Brown LG, Ketchanji M, Nghiem B, Lakely B, Coleman R, Montgomery B, Lange PH, Roudier M, Higano CS, Bielas JH, Nelson PS, Vessella RL, Morrissey C. Epithelial mesenchymal-like transition occurs in a subset of cells in castration resistant prostate cancer bone metastases. *Clin Exp Metastasis.* 2016 Mar;33(3):239-48. [Epub ahead of print].

194. Scher HI, Morris MJ, Stadler WM, Higano CS, Basch E, Fizazi K, Antonarakis ES, Beer TM, Carducci MA, Chi KN, Corn PG, de Bono JS, Creicer R, George DJ, Heath EI, Hussain M, Kelly WK, Liu G, Logothetis C, Nanus D, Stein MN, Rathkopf DE, Slovin SF, Ryan CJ, Sartor O, Small EJ, Smith MR, Sternberg CN, Taplin ME, Wilding G, Nelson PS, Schwartz LJ, Halabi S, Kantoff PW, Armstrong AJ. Trial design and objectives for castration-resistant prostate cancer: Updated recommentations from the Prostate Cancer Clinical Trials Working Group 3. *J Clin Oncol.* 2016 Apr 20;34(12):1402-18.

195. Kumar A, Coleman I, Morrissey C, Zhang X, True LD, Gulati R, Etzioni R, Bolouri H, Montgomery B, White T, Lucas JM, Brown L, Dumpit RF, DeSarkar N, Higano C, Yu EY, Coleman R, Schultz N, Fang M, Lange PH, Shendure J, Vessella RL, Nelson PS. Substantial interindividual and limited intraindividual genomic diversity among tumors from men with metastatic prostate cancer. *Nat Med.* 2016 Apr;22(4):369-78. PMID: 26928463

196. Higano CS, Zarowski C, Wassersug R, Elliott S. Sexual Health After Cancer Therapy. *J Oncol Pract.* 2016 Apr;12(4):305-6. doi: 10.1200/JOP.2016.011536. PMID:27072384

197. Halabi S, Kelly WK, Ma H, Zhou H, Solomon NC, Fizazi K, Tangen CM, Rosenthal M, Petrylak DP, Hussain M, Vogelzang NJ, Thompson IM, Chi KN, de Bono J, Armstrong AJ, Eisenberger MA, Fandi A, Li S, Araujo JC, Logothetis CJ, Quinn DI, Morris MJ, Higano CS, Tannock IF, Small EJ. Meta-Analysis Evaluating the Impact of Site of Metastasis on Overall Survival in Men With Castration-Resistant Prostate Cancer. *J Clin Oncol.* 2016 May 10;34(14):1652-9. doi: 10.1200/JCO.2015.65.7270. Epub 2016 Mar 7. PMID:26951312

198. Chi KN, Yu EY, Jacobs C, Bazov J, Kollmannsberger C, Higano CS, Mukherjee SD, Gleave ME, Stewart PS, Hotte SJ. A phase I dose-escalation study of apatorsen (OGX-427), an antisense inhibitor targeting heat shock protein 27 (Hsp27), in patients with castration-resistant prostate cancer and other advanced cancers. *Ann Oncol.* 2016 Jun;27(6):1116-22. doi: 10.1093/annonc/mdw068. Epub 2016 Feb 18. PMID:27022067

199. Penson DF, Armstrong AJ, Concepcion R, Agarwal N, Olsson C, Karsh L, Dunshee C, Wang F, Wu K, Krivoshik A, Phung D, Higano CS. Enzalutamide Versus Bicalutamide in Castration-Resistant Prostate Cancer: The STRIVE Trial. *J Clin Oncol*. 2016 Jun 20;34(18):2098-106. doi: 10.1200/JCO.2015.64.9285. Epub 2016 Jan 25. PMID:26811535

200. Roudier MP, Winters BR, Coleman I, Lam HM, Zhang X, Coleman R, Chéry L, True LD, Higano CS, Montgomery B, Lange PH, Snyder LA, Srivastava S, Corey E, Vessella RL, Nelson PS, Üren A, Morrissey C. Characterizing the molecular features of ERG-positive tumors in primary and castration resistant prostate cancer. *Prostate*. 2016 Jun;76(9):810-22. doi: 10.1002/pros.23171. Epub 2016 Mar 16. PMID:26990456

201. Beer TM, Armstrong AJ, Rathkopf D, Loriot Y, Sternberg CN, Higano CS, Iversen P, Evans CP, Kim CS, Kimura G, Miller K, Saad F, Bjartell AS, Borre M, Mulders P, Tammela TL, Parli T, Sari S, van Os S, Theeuwes A, Tombal B. Enzalutamide in Men with Chemotherapy-naïve Metastatic Castration-resistant Prostate Cancer: Extended Analysis of the Phase 3 PREVAIL Study. *Eur Urol.* 2016 Jul 28. pii: S0302-2838(16)30437-7. doi: 10.1016/j.eururo.2016.07.032. [Epub ahead of print] PMID:27477525

202. Graff JN, Higano CS, Hahn NM, Taylor MH, Zhang B, Zhou X, Venkatakrishnan K, Leonard EJ, Sarantopoulos J. Open-label, multicenter, phase 1 study of alisertib (MLN8237), an aurora A kinase inhibitor, with docetaxel in patients with solid tumors. *Cancer*. 2016 Aug 15;122(16):2524-33. doi: 10.1002/cncr.30073. [Epub ahead of print] PMID:27192055

203. Evans CP, Higano CS, Keane T, Andriole G, Saad F, Iversen P, Miller K, Kim CS, Kimura G, Armstrong AJ, Sternberg CN, Loriot Y, de Bono J, Noonberg SB, Mansbach H, Bhattacharya S, Perabo F, Beer TM, Tombal B. The PREVAIL Study: Primary Outcomes by Site and Extent of Baseline Disease for Enzalutamide-treated Men with Chemotherapy-naïve Metastatic Castration-resistant Prostate Cancer. *Eur Urol*. 2016 Oct;70(4):675-683. doi: 10.1016 / j.eururo.2016.03.017. [Epub ahead of print] PMID:27006332

204. Cheng HH, Klemfuss N, Montgomery B, Higano CS, Schweizer MT, Mostaghel EA, McFerrin LG, Yu EY, Nelson PS, Pritchard CC. A pilot study of clinical targeted next generation sequencing for prostate cancer: Consequences for treatment and genetic counseling. *Prostate*. 2016 Oct;76(14):1303-11. doi: 10.1002/pros.23219. [Epub ahead of print] PMID:27324988

205. Flaig TW, Potluri RC, Ng Y, Todd MB, Mehra M, Higano CS. Disease and Treatment Characteristics of Men Diagnosed with Metastatic Hormone-Sensitive Prostate Cancer in Real Life: Analysis From a Commercial Claims Database. *Clin Genitourin Cancer*. 2016 Oct 18. doi: 10.10/jclgc.2016.10.002 [Epub ahead of print]

206. Henzler C, Li Y, Yang R, McBride T, Ho Y, Sprenger C, Liu G, Coleman I, Lakely B, Li R, Ma S, Landman SR, Kumar V, Hwant TH, Raf GV, Higano CS, Morrissey C, Nelson PS, Plymate SR, Dehm SM. Truncation and constitutive activation of the androgen receptor by diverse genomic rearrangements in parostate cancer. *Nat Commun*. 2016 Nov 29;7:13668. doi: 10.1039/ncomms13668.

207. Klotz L, Higano CS. Intermittent androgen deprivation therapy: An important treatment option for prostate cancer. *JAMA Oncol*. 2016 Dec 1;2(12):1531-1532. doi:1-.1001/jamaoncol.2016.313. [Epub ahead of print]

208. Smith MR, Antonarakis ES, Ryan CJ, Berry WR, Shore ND, Liu G, Alumkal JJ, Higano CS, Chow Maneval E, Bandekar R, de Boer CJ, Yu MK, Rathkopf DE. Phase 2 Study of the Safety and Antitumor Activity of Apalutamide (ARN-509), a Potent Androgen Receptor Antagonist, in the High-risk Nonmetastatic Castration-resistant Prostate Cancer Cohort. *Eur Urol*. 2016 Dec;70(6):963-970. doi: 10.1016/j.eururo.2016.04.023. [Epub ahead of print] PMID:27160947.

209. Bergstrom CP, Ruffell B, Ho CM, Higano CS, Ellis WJ, Garzotto M, Beer TM, Graff JN. Docetaxel and mitoxantrone before radical prostatectomy in men with high-risk prostate cancer: 10-year follow-up and immune correlates. *Anticancer Drugs*. 2017 Jan;28(1):120-126. [Epub ahead of print].

210. Penson DF, Armstrong AJ, Concepcion R, Agarwal N, Olsson C, Karsh L, Dunshee C, Wang F, Wu K, Krivoshik A, Phung D, Higano CS. Reply to M.A.N. Sendur et al and J. Michels. *J Clin Oncol*. 2017 Jan;35(1):123.

211. Bryce AH, Alumkal JJ, Armstrong A, Higano CS, Iversen P, Sternbert CN, Rathkopf D, Loriot Y, de Bono J, Tomal B, Abhyankar S, Lin P, Krivoshik A, Phung D, Beer TM. Radiographic progression with nonrising PSA in metastatic castration-resistant prostate cancer: post hoc analysis of PREVAIL. *Prostate Cancer Prostatic Dis*. 2017 Jan 24. doi: 10.1038/pcan.2016.71. PMID:28117385.

212. Nguyen HM, Vessella RL, Morrissey C, Brown LG, Coleman IM, Higano CS, Mostaghel EA, Zhang X, True LD, Lam HM, Roudier M, Lange PH, Nelson PS, Corey E. LuCaP Prostate Cancer Patient-Derived Xenografts Reflect the Molecular

Heterogeneity of Advanced Disease and Serve as Models for Evaluating Cancer Therapeutics. *Prostate*. 2017 May;77(6):654-671. doi: 10.1002/pros.23313. PMID: 28156001. PCMID: PMC5354949.

213. Higano CS. The Role of Intermittent Androgen Deprivation Therapy for Prostate Cancer. *J Urol*. 2017 May;197(5):1184-1186.

214. Rosenberg D, Kadokura EA, Bouldin ED, Miyawaki CE, Higano CS, Hartzler AL. Acceptability of Fitbit for physical activity racking within clinical care among men with prostate cancer. *AMIA Annu Symp Proc*. 2017 Feb 10;2016:1050-1059.

215. Chi KN, Higano CS, Blumenstein B, Ferrero JM, Reeves J, Feyerabend S, Gravis G, Merseburger AS, Stenzl A, Bergman AM, Mukherjee SD, Zalewski P, Saad F, Jacobs C, Gleave M, de Bono, JS. Custirsen in combination with docetaxel and prednisone for patients with metastatic castration-resistant prostate cancer (SYNERGY trial): a phase 3, multicenter, open-label, randomized trial. *Lancet Oncol*. 2017 Apr;18(4):473-485. doi: 10.1016/S1470-2045(17)30168-7. PMID: 28283282.

216. Alumkal JJ, Chowdhury S, Loriot Y, Sternberg CN, de Bono JS, Tombal B, Carles J, Flaig TW, Dorff TB, Phung D, Forer D, Noonberg SB, Mansbach H, Beer TM, Higano CS. Effect of Visceral Disease Site on Outcomes in Patients With Metastatic Castration-resistant Prostate Cancer Treated With Enzalutamide in the PREVAIL Trial. *Clin Genitourin Cancer*. 2017 Mar 3. pii: S1558-7673(17)30050-1. doi: 10.1016/j.clgc.2017.02.007. PMID: 28344102.

217. Hedden L, Wassersug R, Mahovlich S, Pollock P, Sundar M, Bell RH, Goldenberg L, Higano CS. Evaluating an educational intervention to alleviate distress amongst men with newly diagnosed prostate cancer and their partners. *BJU Int. 2017* May 2017.

218. Crawford ED, Shore MD, Petrylak DP, Higano CS, Ryan CJ. Abiraterone acetate and prednisone in chemotherapy-naïve prostate cancer patients: rational, evidence and clinical utility. *Ther Adv Med Oncol*. 2017 May;9(5):319-333.

219. Pezaro CJ, Omlin A, Mastris K, ANZUP Consumer Advisory Panel, Attard G, Beer TM, Chi KN, Chowdhury S, Davis ID, Drake CG, de Bono JS, Efstathiou E, Gravis G, Higano CS, Hussain M, James N, Logothetis CJ, Morgans A, Parker C, Ryan CJ, Saad F, Sartor O, Small EF, Sternberg CN, Sweeney CJ, Tannock I, Tombal B, Gillessen S. Precision, complexity and stigma in advanced prostate cancer terminology: it is time to move away from 'castration-resistant' prostate cancer. *Ann Oncol*. 2017 Aug 1;28(8):1692-1694.

220. Rathkopf DE, Smith MR, Ryan CJ, Berry WR, Shore ND, Liu G, Higano CS, Alumkal JJ, Hauke R, Tutrone RF, Saleh M, Chow Maneval E, Thomas S, Ricci DS, Yu MK, De Boer CJ, Trinh A, Kheoh T, Bandekar R, Scher HI, Antonarakis ES. Androgen receptor mutations in patients with castration-resistant prostate cancer treated with apalutamide. *Ann Oncol*. 2017 Sep 1;28(9):2264-2271.

221. Alumkal JJ, Chowdhury S, Loriot Y, Sternberg CN, de Bono JS, Tombal B, Carles J, Flaig TW, Dorff TB, Phung, Forer D, Noonberg SB, Mansbach H, Beer TM, Higano CS. Effect of Visceral Disease Site on Outcomes in Patients With Metastatic Castration-resistant Prostate Cancer Treated With Enzalutamide in the PREVAIL Trial. *Clin Genitourin Cancer*. 2017 Oct;15(5):610-617.e3.

222. Hedden L, Wassersug R, Mahovlich S, Pollock P, Sundar M, Bell RH, Goldenberg L, Higano CS. Evaluating an educational intervention to alleviate distress amongst men with newly diagnosed prostate cancer and their partners. *BJU Int*. 2017 Nov;120(5B):E21-E29.

223. Sonpavde G, Pond GR, Plets M, Tangen CM, Hussain M, Lara PN Jr, Goldkorn A, Garzotto MG, Mack PC, Higano CS, Vogelzang NJ, Thompson IM Jr, Twardowski PW, Van Veldhuizen PJ Jr, Agarwal N, Carducci MA, Mond JP, Quinn DI. Validation of the Association of RECIST Changes with Survival in Men with Metastatic Castration-Resistant Prostate Cancer Treated on SWOG Study S0421. *Clin Genitourin Cancer*. 2017 Dec;15(6):635-641.

224. Gillessen S, Attard G, Beer TM, Beltran H, Bossi A, Bristow R, Carver B, Castellan D, Chung BH, Clark N, Daugaard G, Davis I, de Bono J, dos Reis RB, Drake CG, Eeles R, Efstathiou E, Evans C, Fanti S, Feng F, Fizazi K, Frydenberg M, Gleave M, Halabi S, Heidenreich A, Higano CS, James N, Kantoff P, Kellokumpu-Lehtinen PL, Khauli RB, Kramer G, Logothetis C, Maluf F, Morgans AK, Morria M, Mottet N, Murthy V, Oh W, Ost P, Padhani A, Parker C, Pritchard CC, Roach MA, Rubin M, Ryan C, Saad F, Sartor O, Scher HI, Sella A, Shore N, Smith MR, Soule H, Sternberg CN, Suzuki H, Sweeney C, Sydes MR, Tannock I, Tombal B, Valdagni R, Wiegel T. Management of patients with advanced prostate cancer: The report of the Advanced Prostate Cancer Consensus Conference APCCC 2017. *Eur Urol*. 2018 Feb;73(2):178-211.

225. Cheng HH, Plets M, Li H, Higano CS, Tangen CM, Agarwal N, Vogelzang NJ, Hussain M, Thompson IM Jr, Tewari M, Yu EY. Circulating microRNAs and treatment response in the Phase II SWOG S0925 study for patients with new metastatic hormone-sensitive prostate cancer. *Prostate*. 2018 Feb;78(2):121-127.

226. Stein CA, Levin R, Given R, Higano CS, Nemeth P, Bosch B, Chapas-Reed, J, Dreicer R. Randomized phase 2 therapeutic equivalence study of abiraterone acetate fine particle formulation vs. originator abiraterone acetate in patients with metastatic castration-resistant prostate cancer: The STAAR study. *Urol Oncol*. 2018 Feb;36(2):81.e9-81.e16.

227. Hirata Y, Morino K, Akakura K, Higano CS, Aihara K. Personalizing androgen suppression for prostate cancer using mathematical modeling. *Sci Rep*. 2018 Feb 8;8(1):2673.

228. Rathkopf DE, Beer TM, Loriot Y, Higano CS, Armstrong AJ, Sternberg CN, de Bono JS, Tombal B, Parli T, Bhattacharya S, Phung, Krivoshik A, Scher JI, Morris MJ. Radiographic progression-free survival as a clinically meaningful end point in metastatic castration-resistant prostate cancer: The PREVAIL randomized clinical trial. *JAMA Oncol*. 2018 May 1;4(5):694-701.

229. Hahn AW, Higano CS, Taplin ME, Ryan CJ, Agarwal N. Metastatic Castration-Sensitive Prostate Cancer: Optimizing Patient Selection and Treatment. *Am Soc Clin Oncol Educ Book*. 2018 May 23;(38):363-371.

230. Unger JM, Griffin K, Donaldson GW, Baranowski KM, Good MJ, Reburiano E, Hussain M, Monk PJ, Van Veldhuizen PJ, Carducci MA, Higano CS, Lara PN, Tangen CM, Quinn DI, Wade JL III, Vogelzang NJ, Thompson IM Jr, Moinpour CM. Patient-reported outcomes for patients with metastatic castration-resistant prostate cancer receiving docetaxel and Atrasentan versus docetaxel and placebo in a randomized phase III clinical trial (SWOG S0421). *J Patient Rep Outcomes*. 2018 Jun 13;2:27.

231. Higano CS. Does nonmetastatic castration-resistant prostate cancer still exist? Nat Rev Clin Oncol. 2018 Jun;15(6):350-351.

232. Cherrier M, Cross DJ, Higano CS, Minoshima S. Changes in cerebral metabolic activity in men undergoing androgen deprivation therapy for non-metastatic prostate cancer. *Prostate Cancer Prostatic Dis*. 2018 Sep;21(3):394-402.

233. Armstrong AJ, Lin P, Higano CS, Sternberg CN, Sonpavde G, Tombal B, Templeton AJ, Fizazi K, Phung D, Wong EK, Krivoshik A, Beer TM. Development and validation of a prognostic model for overall survival in chemotherapy-naïve men with metastatic castration-resistant prostate cancer. Ann Oncol. 2018 Sep 10.

234. Crawford ED, Schellhammer PF, McLeod DG, Moul JW, Higano CS, Shore N, Denis L, Iversen P, Eisenberger MA, Labrie F. Androgen receptor-targeted treatments for prostate cancer: 35 years' progress with antiandrogens. *J Urol*. 2018 Nov;200(5):956-966. Review.

INVITED EDITORIALS OR REVIEWS

1. Higano CS, Raskind WH, Singer JW. Use of interferon alfa-2a to treat hematologic relapse of chronic myelogenous leukemia after bone marrow transplantation. *Acta Haematol.* 1993 89:8-14.

2. Higano CS. Alpha interferon therapy of minimal residual disease after allogeneic bone marrow transplantation for chronic myelogenous leukemia. *Interferons and Cytokines.* 1994 25:6-8.

3. Appelbaum FA, Clift CD, Buckner CD, Anasetti C, Radich J, Higano CS, Storb R, Hansen J, Thomas ED. Allogeneic marrow transplantation for chronic myeloid leukemia. *Med Oncol.* 1994 11:69-74.

4. Higano CS. Therapeutic options for prostate cancer patients who progress after initial hormonal therapy. *Clin Care Prostatic Dis.* 1995 3:1-4.

5. Higano CS. Strategies for the management of advanced prostate cancer, Case Study #1. The Postgraduate Institute for Medicine, July 1998.

6. Higano CS. Strategies for the management of advanced prostate cancer, Case Study #2. The Postgraduate Institute for Medicine, September 1998.

7. Dawson N, Moul J, Higano CS. Hormone refractory prostate cancer: current issues and treatment options. Monograph, Physicians and Scientists Publishing Company, Spring, 1999.

8. Higano CS. "Making a difference in hormone refractory prostate cancer" in New Frontiers in the Diagnosis and Treatment of Prostate Diseases, Medical Education Collaborative, 1999, 2000 and 2001, 2002, 2003 editions.

9. Gleave ME, Higano C, Glode LM, Goluboff E, Pummer K, Crawford ED. New horizons in the management of hormone-refractory prostate cancer. *Reviews in Urology.* 2001 (suppl): 40-48.

10. Higano CS. Side effects of androgen deprivation therapy: monitoring and minimizing toxicity. *Urology.* 2003 61(2 suppl 1):32-38.

11. Saad F, D'Elia F, DiTrolio J, Eastham J, Gheiler E, Guise T, Higano CS, et al. The role of IV bisphosphonates in the management of bone complications related to prostate cancer: a consensus from experts. Monograph, Strategic Institute for Continuing Health Care Education, 2003.

12. Higano CS. Androgen-deprivation therapy for prostate cancer. *Clin Prostate Cancer.* 2003 2(1):22-23.

13. Carroll PR, Benaron DA, Blackledge G, Coakley FV, D'Amico AV, Higano CS, Iversen P, Kattan M, Nanus DM, Nelson JB, Oh WK, Roach M 3rd, Sellers WR, Smith MR, McMann MC, Kantoff PW. Overview consensus statement. Third International Conference on Innovations and Challenges in Prostate Cancer: Prevention, Detection, and Treatment. *J Urol.* 2003 170(6 Pt 2):S3-S5.

14. Higano CS. Bone loss and the evolving role of bisphosphonate therapy in prostate cancer. *Urol Oncol.* 2003 21(5):392-398.

15. Higano CS. Management of bone loss in men with prostate cancer. *J Urol.* 2003 170(6 Pt 2):S59-S64.

16. Higano CS. Understanding treatments for bone loss and bone metastases in patients with prostate cancer: a practical review and guide for the clinician. *Urol Clin North Am.* 2004 31(2):331-352.

17. Higano CS. Holzbeierlein/Castle/Thrasher article reviewed (*Oncology* 2004, 18:303-309). *Oncology.* 2004 18:319-321.

18. Higano CS. Current status of treatment for patients with metastatic prostate cancer. *Can J Urol.* 2005 12 Suppl 2:38-41.

19. Higano C. Androgen deprivation therapy: monitoring and managing the complications. *Hematol Oncol Clin North Am.* 2006 20(4):909-923.

20. Wright JL, Higano CS, Lin DW. Intermittent androgen deprivation: Clinical experience and practical applications. *Urol Clin North Am.* 2006 33(2):167-179.

21. Cookson MS, Aus G, Burnett A, Canby-Hagino ED, D'Amico AV, Dmochowski RR, Eton DT, Forman JD, Goldenberg SL, Hernandez J, Higano CS, Kraus S, Moul JW, Tangen C, Thrasher JB, Thompson I. Variation in the definition of biochemical recurrence in patients treated for localized prostate cancer: the AUA prostate guidelines for localized prostate cancer update panel report and recommendations for a standard in the reporting of surgical outcomes. *J Urol.* 2007 177(2):540-545.

22. Higano CS. Annual Zoledronic Acid: Is Less More? *J Clin Oncol.* 2007 25(9):1026.

23. Burnett AL, Aus G, Canby-Hagino ED, Cookson MS, D'Amico AV, Dmochowski RR, Eton DT, Forman JD, Goldenberg SL, Hernandez J, Higano CS, Kraus S, Liebert M, Moul JW, Tangen C, Thrasher JB, Thompson I, American Urological Association Prostate Cancer Guideline Update Panel. Erectile function outcome reporting after clinically localized prostate cancer treatment. *J Urol.* 2007 178(2):597-601.

24. Basch E, Somerfield M, Beer T, Carducci MA, Higano CS, Hussain MHA Scher HI. American Society of Clinical Oncology endorsement of the Cancer Care Ontario Practice Guideline on non-hormonal therapy for men with metastatic hormone-refractory (castration-resistant) prostate cancer. *J Clin Oncol.* 2007 25(33):5313-5318.

25. Higano CS. Androgen-deprivation-therapy-induced fractures in men with nonmetastatic prostate cancer: what do we really know? *Nat Clin Pract Urol.* 2008 5(1):24-34.

26. Zerbib M, Zelefsky MJ, Higano CS, Carroll PR. Conventional treatments of localized prostate cancer. *Urology.* 2008 72(Suppl 6A):S25-35.

27. Higano CS. Positive surgical margins: the argument for androgen deprivation and chemotherapy. *Urol Oncol.* 2009 27(1):89-91.

28. Dean JP, Higano CS. Does chemotherapy have a role before hormone-resistant disease develops? *Curr Urol Rep.* 2009 10(3):226-235.

29. Higano CS, Small EJ, Schellhammer P, Yasothan U, Gubernick S, Kirkpatrick P, Kantoff PW: Sipuleucel-T. *Nat Rev Drug Discov.* 2010 July;9(7):513-514.

30. Higano CS, Crawford ED. New and emerging agents for the treatment of castration-resistant prostate cancer. *Urol Oncol.* 2011 Nov/Dec;29(6s):S1-S8.

31. Sonpavde G, Di Lorenzo G, Higano CS, Kantoff PW, Madan R, Shore ND. The role of sipuleucel-T in therapy for castration-resistant prostate cancer: a critical analysis of the literature. *Eur Urol.* 2012 Apr;61(4):639-647.

32. Kantoff P, Higano CS. Integration of immunotherapy into the management of advanced prostate cancer. *Urol Oncol.* 2012 Sep-Oct;30(5 Suppl):S41-7.

33. Higano CS . Sexuality and Intimacy After Definitive Treatment and Subsequent Androgen Deprivation Therapy for Prostate Cancer. *J Clin Oncol.* 2012 Oct 20;30(30):3720-5. doi: 10.1200/JCO.2012.41.8509. Epub 2012 Sep 24. Review. Erratum in: *J Clin Oncol.* 2013 Feb 20;31(6):824.

34. Quinn DI, Vaishampayan U, Higano CS, Lin DW, Shore ND, Beer TM. Sequencing therapy in advanced prostate cancer: focus on sipuleucel-T. *Expert Rev Anticancer Ther.* 2014 Jan;14(1):51-61.

35. Higano CS. Intermittent versus continuous androgen deprivation therapy. *J Natl Compr Canc Netw.* 2014 May;12(5):727-33.

36. Higano CS. New developments in the treatment of castration-resistant prostate cancer. *J Natl Compr Canc Netw.* 2014 May;12(5 Suppl):773-6.

37. Higano CS. The Role of Intermittent Androgen Deprivation Therapy for Prostate Cancer. *J Urol.* 2017 May;197(5):1184-1186.

38. Higano CS. Does nonmetastatic castration-resistant prostate cancer still exist? *Nat Rev Clin Oncol.* 2018 Jun;15(6):350-351.

BOOK CHAPTERS

1. Russell KJ, Higano CS, Boileau MA, Russell AH, Collins C, Koh WJ, Chapman W, Griffin TW. Combined 5-fluorouracil and irradiation for the treatment of invasive bladder cancer. In *Medical Radiology - Diagnostic Imaging and Radiation Oncology.* Volume entitled Concomitant Continuous Infusion Chemotherapy and Radiation, M Rotman and CJ Rosenthal (eds). Springer-Verlag, Berlin, 175-180, 1991.

2. Higano CS, Lange PH. Testicular cancer surveillance and follow-up: Counterpoint. In *Cancer Patient Follow-up*, F Johnson (ed). Mosby, 1996.

3. Nelson P, Higano CS. Management of hormone refractory prostate cancer: chemotherapy and immunotherapy. In *Advanced Therapy of Prostate Disease*. Martin Resnick and Ian Thompson (eds.). B.C. Decker, Inc., Hamilton, 385-404, 2000.

4. Veatch A, Higano CS. Prostate specific antigen and chemotherapy. In *Prostate Specific Antigen,* Michael K. Brawer (ed.) Marcel Dekker, 261-282, 2001.

5. Higano CS. Bone metastases in hormone-refractory prostate cancer. In *Treatment Reporter & "Ask the Experts" audio edition,* Projects in Knowledge, 2003.

6. Higano CS, Thompson IM, Sylvester JE. Will I have to have hormones? In *The Prostate Cancer Treatment Book.* P Grimm, J Blasko, J Sylvester (eds.). McGraw-Hill/Contemporary Books, 155-165, 2003.

7. Higano CS, Friedland JL, Beyer DC, Shinohara K, Blasko JC. What happens if the cancer returns? In *The Prostate Cancer Treatment Book.* P Grimm, J Blasko, J Sylvester (eds.). McGraw-Hill/Contemporary Books, 167-176, 2003.

8. Roudier MP, Corey E, True LD, Higano CS, Ott SM, Vessella RL. Histological, immunophenotypic, and histomorphometric characterization of prostate cancer bone metastases. In *The Biology of Skeletal Metastases.* Keller ET and Chung LW (eds). Kluwer Academic Publishers, Boston, MA. 311-339, 2004.

9. Higano CS. Counseling patients on choice of therapy: Medical Oncologist perspective. In *Management of Prostate Cancer*, Eric Klein (ed). Humana Press, 491-500, 2004.

10. Higano CS, Frohlich MW. Sipuleucel-T (APC8015): Active cellular immunotherapy for advanced metastatic androgen-independent prostate cancer. In *Drug Management of Prostate Cancer*, Figg W, Small E, and Chau C (eds). Humana Press. In press. 2009.

11. Jonasch E, Sieflker-Radtke A, Yu EY, Higano CS, Tsu MS, Hey D, Thompson J. Genitourinary oncology. In: Lin EH, editor – a multidisciplinary cancer-matrix manual. Madison: Advanced Medical Publishing. 2010.

12. Chi KN, Nguyen PL, Higano CS. Androgen Deprivation for Prostate Cancer. In: *Am Soc Clin Oncol Educ Book*. 2013:176-183. doi: E10.1200/EdBook_AM.2013.33.e176.

ABSTRACTS

1. Higano CS, Gharib H, Zinsmeister AR, Dickson ER. Increased prevalence of thyroid disease and hypothyroidism in a primary biliary cirrhosis. Abstracts of the American Thyroid Association; T-45, October 1983.

2. Higano CS, Livingston RB. Intravenous methotrexate and oral dipyridamole in the treatment of refractory solid tumors: A pilot study. *Proc Am Soc Clin Onc* 4:44, 1985. Presented at ASCO Annual Meeting, Houston, May 1985.

3. Mortimer J, Higano CS. Continuous infusion 5-fluorouracil and folinic acid in disseminated colorectal cancer: A phase I-II study. *Proc Am Assoc Cancer Res* 26:171, 1985. Presented at ASCO Annual Meeting, Los Angeles, May 1986.

4. Collins C, Higano CS, Miller T, Livingston RB. Cyclophosphamide, vincristine, platinum and etoposide and radiation therapy for extensive small cell lung cancer: A Southwest Oncology Group study. *Proc Am Soc Clin Oncol* 5:181, 1986. Presented at ASCO Annual Meeting, Los Angeles, May 1986.

5. Abdel-Nabi H, Schwartz AN, et al. Preliminary studies of In-III-labeled ZCE 025 monoclonal immunoscintigraphy in metastatic colorectal carcinoma. Presented at 33rd Annual Meeting of Society of Nuclear Medicine, Washington, June 1986.

6. Abdel-Nabi H, Schwartz A, Matsuoka D., Wechter D, Langdale L, Cerqueira M, Higano CS. Presented at 27th Annual Meeting, Southeastern Chapter of the Society of Nuclear Medicine, Nashville, November 1986.

7. Abdel-Nabi H, Schwartz AN, Higano CS, Unger MW. Detection of metastatic colorectal carcinoma with In-III-ZCE 025 monoclonal antibody. Presented at 72nd Scientific Assembly of the Radiologic Society of North America, December 1986.

8. Abdel-Nabi H, Schwartz A, Matsuoka D, Wechter D, Langdale L, Cerqueira M, Higano CS: A new diagnostic tool to detect colorectal carcinoma. Presented at Veterans Affairs National R&D Conference, Las Vegas, December 1986.

9. Higano CS, Livingston RB Intravenous methotrexate and oral dipyridamole in the treatment of refractory solid tumors: A phase I-II study. *Proc Am Soc Clin Onc* 6:23, 1987. Presented at ASCO Annual Meeting, Atlanta, May 1987.

10. Boileau M, Russell K, Ireton R, Collins C, Higano CS. Bladder preservation: Neoadjuvant 5-fluorouracil and irradiation as primary management of invasive bladder cancer. Presented at Northwest Urological Society, Portland, December 1987.

11. Russell K, Boileau M, Ireton R, Koh WJ, Russell AH, Chapman W, Higano CS, Collins C, Griffin T. Histologic clearance of invasive transitional cell carcinoma of the bladder with combined infusion of 5-fluorouracil and irradiation: Alternative to cisplatin neoadjuvant strategies. Presented at Radiologic Society of North America Annual Meeting, December 1987.

12. Collins C, Russell KJ, Boileau MA, Higano CS. A pilot study of neoadjuvant 5-fluorouracil and irradiation in the treatment of bladder cancer. *Proc Am Soc Clin Onc* 7:122. Presented at ASCO Annual Meeting, 1988.

13. Higano CS, Raskind W, Singer JW. Relapse of chronic myelogenous leukemia after allogeneic marrow transplantation: Treatment with recombinant interferon alpha. *Proc Am Soc Clin Onc* 7:179. Presented at ASCO Annual Meeting, 1988.

14. Mortimer JE, Chestnut J, Higano CS, Goodman G. High dose cisplatin in metastatic melanoma: Comparison of two dose schedules. *Proc Am Soc Clin Onc* 7:254. Presented at ASCO Annual Meeting, 1988.

15. Higano CS, Raskind W, Durnam D, Singer J. Relapse of CML after allogeneic marrow transplantation: Treatment with recombinant interferon alpha, an update. *Proc Am Soc Clin Onc* 8:209. Presented at ASCO Annual Meeting, 1989.

16. Higano CS, Crowley J, Livingston RB. Weekly Cisplatin based induction for extensive non-small cell lung cancer with Cisplatin and VP-16 Consolidation. *Proc Am Soc Clin Onc* 8:227. Presented at ASCO Annual Meeting, 1989.

17. Higano CS, Craig J, Goodman P, Blumenstein B, Wettlaufer J, Crawford ED. A phase II trial of amonafide in advance renal cell carcinoma. *Proc Am Soc Clin Onc* 8:147. Presented at ASCO Annual Meeting, 1989.

18. Russell KJ, Boileau MA, Ireton RC, Higano CS, Collins C, Koh WJ, Griffin BR, Chapman WH, Griffin TW. Transitional cell carcinoma of the urinary bladder. Histologic clearance with combined 5-FU chemotherapy and radiation therapy. *Urology/Nephrology Digest* 2:25-26, 1989.

19. Higano CS, Raskind W, Durnam D, Singer J. Alpha interferon induces cytogenetic remissions in patients who relapse with chronic myelogenous leukemia after allogeneic bone marrow transplantation. *Blood* 74(7) Suppl 1:83a. Presented at American Society of Hematology Annual Meeting, December 1989.

20. Russell K, Higano CS, Boileau M, Russell A, Collins C, Koh W, Chapman W, Griffin T. Combined 5-Fluorouracil and irradiation for the treatment of invasive bladder cancer. *Proc Am Soc Thera Rad Oncol* 17(Supp):165. Presented at ASTRO Annual Meeting, 1989.

21. Higano CS, Raskind W, Durnam D, Singer JW. Alpha interferon induces cytogenetic remissions in patients who relapse with chronic myelogenous leukemia after allogeneic bone marrow transplantation. *J Cell Biochem* 14A(Supp), 1990. Presented at UCLA Symposium on Strategies in Bone Marrow Transplantation, Los Angeles, January 1990.

22. Singer JW, Nemunaitis J, Buckner CD, Epstein DC, Higano CS, Storb R, Thomas ED, Appelbaum FR. Phase I/II trial of rhGM-CSF after allogeneic bone marrow transplantation (BMT). Presented at UCLA Symposium on Strategies in Bone Marrow Transplantation, Los Angeles, January 1990.

23. Nemunaitis J, Singer JW, Buckner CD, Epstein CD, Higano CS, Storb R, Thomas ED, Appelbaum FR. Phase III trial of rhGM-CSF in autologous bone marrow transplant patients with lymphoid malignancy. Presented at UCLA Symposium on Strategies in Bone Marrow Transplantation, Los Angeles, January 1990.

24. Higano CS, Brixey M, Lee K, Boileau M, Livingston RB. Initial chemohormonal therapy for D2 prostate cancer. *Proc Am Soc Clin Onc* 9:149. Presented at ASCO Annual Meeting, May 1990.

25. Nemunaitis J, Meyers JD, Buckner CD, Bianco JC, Groves E, Higano CS, Shulman H, Storb R, Hansen J, Appelbaum FR, Singer JW. Phase I/II trial of recombinant human macrophage-colony stimulating factor in patients with invasive fungal infection. Presented at International Society of Hematology 23rd Congress/American Society of Hematology 32nd Annual Meeting, 1990.

26. Higano CS, Raskind W, Durnam D, Singer JW. Interferon alpha induces cytogenetic remissions in patients who relapse with chronic myelogenous leukemia after allogeneic bone marrow transplantation. *Experimental Hematology* 18(6):645, July 1990. Presented at International Society of Experimental Hematology, August 1990.

27. Singer JW, Nemunaitis J, Buckner CD, Epstein C, Higano CS, Storb R, Thomas ED, Appelbaum FR. Phase I/II trial of rhGM-CSF after allogeneic bone marrow transplantation. *J Cell Biochem*, suppl 14A:333, 1990.

28. Jacobson AF, Teefey SA, Bianco JA, Higano CS. Comparison of sonography and scintigraphy for determination of changes in gall bladder volume following administration of cholecystokinin octapeptide (sincalide). Presented at Society of Nuclear Medicine 38th Annual Meeting, Cincinnati, 1991.

29. Jacobson AF, Teefy SA, Lee SP, Hollister MS, Higano CS, Bianco, JA. Delay in gall bladder visualization of hepatobiliary scintigraphy following bone marrow transplantation in the absence of acute cholecystitis: association with sludge formation and oral intake. *J Nucl Med* 32:1047, 1991. Presented at Society of Nuclear Medicine 38th Annual Meeting, Cincinnati, 1991.

30. Jacobson AF, Teefey SA, Higano CS, Bianco JA. Utility of increased lung uptake of Tc-99m sulfur colloid as an early indicator of the development of hepatic venoocclusive disease in bone marrow transplant patients. Presented at Radiological Society of North America 77th Annual Meeting, Chicago, 1991.

31. Hommeyer SC, Teefey SA, Jacobson AF, Higano CS, Bianco JA, McDonald GB, Colacurcio CJ. Veno-occlusive disease of the liver: Evaluation with ultrasound. Presented at Radiological Society of North America 77th Annual Meeting, Chicago, 1991.

32. Higano CS, Raskind W, Singer JW. Alpha interferon treatment of chronic myelogenous leukemia in relapse after allogeneic marrow transplantation. A prospective trial. *Blood* 78:119, 1991. Presented at American Society of Hematology Annual Meeting, December 1991.

33. Thirlwell M, Leyland-Jones B, Rodgers A, Langleben A, Shields A, Higano CS, Trudeau M, Ahlgren P, Wilhelm DJ. Open randomized dose-finding study of gallium nitrate administered intravenously in malignant hypercalcemia. *Proc Am Soc Clin Onc* 11:396. Presented at ASCO Annual Meeting, 1992.

34. Hollister MS, Teefy SA, Lee SP, Jacobson AF, Higano CS, Bianco JA, Colacurcio CJ. Gallbladder stasis and contractility: their role in sludge formation in bone marrow transplant patients. Presented at Society of Gastrointestinal Radiologists 21st Annual Meeting, Orlando, 1992.

35. Wiseman GA, Higano CS, Graham MM. Bone scan false positive lesions in patients with stage D2 prostate adenocarcinoma during initial treatment with combined hormone and chemotherapy. Presented at Society of Nuclear Medicine 40th Annual Meeting, June 1993.

36. Higano CS, Raskind W, Singer JW. Alpha interferon treatment of cytogenetic-only relapse of chronic myelogenous after marrow transplantation. *Proc Am Soc Clin Oncol* 12:307. Presented at ASCO Annual Meeting, 1993.

37. Higano CS, Raskind W, Flowers M. Alpha interferon results in high complete cytogenetic response rate in patients with cytogenetic-only relapse of chronic myelogenous leukemia after marrow transplantation. *Blood* 82:661, 1993. Presented at American Society of Hematology Annual Meeting, St. Louis, December 1993.

38. Flowers MED, Sullivan KM, Martin P, Buckner CD, Beach K, Higano CS, Radich J, Clift R, Bensinger W, Deeg HJ, Chauncey T, Rowley S, Storb R, Appelbaum F. G-CSF stimulated donor peripheral blood infusions in patients with hematologic malignancies relapsing after allogeneic transplantation. *Blood* 86 Suppl 1:2242, 1995.

39. Higano CS, Chielens D, Bryant E, Raskind W, Radich J, Flowers M: Alfa-2a-interferon produces durable cytogenetic responses in patients with cytogenetic relapse of chronic myelogenous leukemia after marrow transplantation. *Blood* 86 Suppl 1:2253, 1995. Presented at American Society of Hematology Annual Meeting, Seattle, December 1995.

40. Higano CS, Ellis WJ, Lange PH. Intermittent androgen suppression for treatment of prostate cancer: the Seattle pilot experience. *Proc Am Soc Clin Oncol* 15: 610, 1996. Presented at ASCO Annual Meeting, Philadelphia, May 1996.

41. Higano CS, Chielens D. Alfa interferon and cis-retinoic acid in combination for treatment of hormone refractory prostate cancer. *Proc Am Soc Clin Oncol* 15: 611, 1996. Presented at ASCO Annual Meeting, Philadelphia, May 1996.

42. Higano CS, Bushnell D, Quick D, Eary J. Interim results of a phase I-II trial of high dose samarium-153 EDTMP in conjunction with total androgen blockade for patients with newly diagnosed prostate cancer with bone metastases. *Proc Am Soc Clin Oncol*. Presented at ASCO Annual Meeting, 1998.

43. Higano CS, Chielens D, Radich J, Flowers M, Applebaum FR. Adjuvant treatment with alpha interferon for patients at high risk for relapse after allogeniec bone marrow transplantation for chronic myelogenous leukemia. *Blood* 92:10 Suppl 1:654a. Presented at American Society of Hematology Annual Meeting, Miami, December 1998.

44. Higano CS, Stephens C, Nelson PS, Fearne V, Davies C, Russell K, Ellis WJ, Lange PH. Prospective serial measurements of bone mineral density in prostate cancer patients without bone metastases who are treated with intermittent androgen suppression. *Proc Am Soc Clin Oncol*, 1999. Presented at ASCO Annual Meeting, Atlanta, May 1999.

45. Buhler KR, Quinn JE, True LD, Whitney SC, Odman AM, Ellis WJ, Lange PH, Higano CS, Vessella RL. The LuCaP series of xenografts--LuCaP 35, LuCaP p 41, and LuCaP 49. Presented at AACR Annual Meeting, San Francisco, March 2000.

46. Higano CS, Small EJ, Sosman J, Vogelzang NJ, Caron D. Safety and Biologic Activity of multiple cycles of Flt3 Ligand in patients with bone scan negative hormone refractory prostate cancer. *Proc Am Soc Clin Oncol* 2000. Presented at ASCO Annual Meeting, New Orleans, May 2000.

47. Roudier M, Higano CS, True LD, Ott-Ralph S, Penson DF, Vessella RL, Lange PH. Evaluation of Concordance Between Bone Histology and Tc-99 Methylene Diophosphonate Bone Scan in Advanced Prostate Cancer Patients with Special Reference to Bisphosphonate Treatment. Presented at AACR Annual Meeting, San Francisco, April 2000.

48. Wang Z, Hass GM, True LD, Higano CS, Tisdale MJ, Vessella RL. Differential expression of the human cachexia-associated protein gene and protein in prostate cancer. Presented at AACR Annual Meeting, New Orleans, March 2001.

49. Wang Z, Hass GM, True LD, Higano CS, Tisdale MJ, Vessella RL. Differential expression of the human cachexia-associated protein gene and protein in prostate cancer. Presented at ASCO Annual Meeting, San Francisco, May 2001.

50. Higano CS, Veatch A, Gonzalez M, Cherrier M. The effects of combined androgen blockade on cognitive function in patients with biochemical relapse of prostate cancer. *Proc Am Soc Clin Oncol* 2001 20:168b. Presented at American Urological Association Annual Meeting, Anaheim, June 2001. Chosen as one of top 120 meeting abstracts.

51. Roudier M, Higano CS, True LD, Ott SM, Vesselle H, Lange PH, Vessella RL. Skeletal involvement in 14 advanced prostate cancer patients, 5 of them treated by Pamidronate. Presented at ASBMR meeting, Phoenix, October 2001.

52. Corey E, Quinn JE, Brown LG, Roudier MPM, Higano CS, Vessella RL. Examination of effects of Zoledronic Acid on prostate cancer. *J Bone Miner Res* 16:S192, #F070, 2001. Presented at ASBMR meeting, Phoenix, October 2001.

53. Cherrier MM, Gonzales MT, Kung D, Mau M, Veatch A, Higano CS. Assessment of cognition in patients with prostate cancer without bone metastases treated with intermittent androgen suppression. Society for Neuroscience Abstracts 2001 27:247.12. Presented at Society for Neuroscience Meeting, San Diego, November 2001.

54. Pfitzenmaier J, Vessella RL, Higano CS, Noteboom JL, Wallace D, Corey E. Cachectic prostate cancer patients present with elevated cytokine levels. Presented at AACR Annual Meeting, San Francisco, April 2002.

55. Jiang PYZ, Miller MJ, Pitzel MM, Jensen ML, Higano CS. Prospective Evaluation of BMD in Prostate Cancer Patients Without Bone Metastases Treated With Intermittent Androgen Suppression Therapy. Presented at 3rd North American Symposium on Skeletal Complications of Malignancy, Bethesda, April 2002.

56. Roudier M, Ott-Ralph SM, True LD, Higano CS, Vessella RL. Heterogeneity of prostate cancer bone metastases. Presented at 3rd North American Symposium on Skeletal Complications of Malignancy, Bethesda, April 2002.

57. Roudier M, Ott-Ralph SM, True LD, Higano CS, Vessella RL. Pamidronate treatment and bone volume in patients with prostate cancer bone metastases. Presented at: 3rd North American Symposium on Skeletal Complications of Malignancy, Bethesda, April 2002.

58. Jiang PYZ, Miller MJ, Stern J, Pitzel MM, Higano CS. The dynamics of bone mineral density during intermittent androgen suppression in prostate cancer patients without bone metastases. *Proc Am Soc Clin Onc*, 2001 21:198a. Presented at ASCO Annual Meeting, Orlando, May 2002.

59. Beer TM, Garzotto M, Lowe BA, Ellis WJ, Lange PH, Montalto MA, Higano CS. Phase I study of weekly docetaxel and mitoxantrone prior to neoadjuvant in patients with high risk localized prostate cancer. *Proc Am Soc Clin Onc*, 2001 21:155b. Presented at ASCO Annual Meeting, Orlando, May 2002.

60. Ewer MS, Vooletich M, Valero V, Higano CS, Benjamin RS. Trastuzumab (herceptin) cardiotoxicity: clinical course and cardiac biopsy correlations. *Proc Am Soc Clin Onc*, 2001 21:123a. Presented at ASCO Annual Meeting, Orlando, May 2002.

61. Rose A, Cherrier M, Ahlgren A, Miller M, Higano CS. The effects of intermittent androgen suppression on cognitive function in patients with biochemical relapse of prostate cancer. *Proc Am Soc Clin Onc*, 2002 21:163b. Presented at ASCO Annual Meeting, Orlando, May 2002.

62. Schellhammer PF, Small EJ, Higano CS, Nemunaitis J, Peshwa MV, Jones L, Strang G, Valone FH. Autologous dendritic cells pulsed with prostatic acid phosphatiase (APC8015) for hormone refractory prostate cancer: a phase III randomized, double blind, placebo controlled trial. *Proc Am Soc Clin Onc*, 2001 21:183a. Presented at ASCO Annual Meeting, Orlando, May 2002.

63. Small EJ, Schellhammer PF, Higano CS, Peshwa MV, Nemunaitis J, Jones L, Valone FH. A phase III randomized, double-blind, placebo-controlled trial of autologous dendritic cells pulsed with prostatic acid phosphatase (APC8015) in men with asympotomatic, metastatic, hormone refractory prostate cancer. Presented at American Urological Association Annual Meeting, Orlando, May 2002.

64. Pfitzenmaier J, Corey E, Higano CS, Noteboom JL, Wallace D, Lange PH, Vessella R. Elevated cytokines in prostate cancer patients with cachexia. Presented at American Urological Association Annual Meeting, Orlando, May 2002.

65. Kylstra JW, Small EJ, Schellhammer PF, Higano CS, Nemunaitis J, Redfern C, Valone FH. Immunotherapy (APC8015, Provenge) in hormone refractory prostate cancer: phase III study results. Presented at CaP CURE 9th Annual Scientific Retreat, Washington, September 2002.

66. Beer TM, Garzotto M, Lowe BA, Ellis WJ, Lange PH, Montalto MA, Higano CS. Weekly docetaxel and mitoxantrone prior to prostatectomy in patients with high risk localized prostate cancer. *J Urol* 2003, 169(4 suppl):444. Presented at ASCO Annual Meeting, Chicago, May 2003.

67. Small EJ, Rini B, Higano CS, Redfern C, Nemunaitis J, Valone F, Kylstra J, Schellhammer PF. A randomized, placebo-controlled phase III trial of APC8015 (Provenge™) in patients with androgen-independent prostate cancer. Presented at ASCO Annual Meeting, Chicago, May 2003.

68. Gulley JL, Figg WD, Carter J, Fedenko K, Arien PM, Hussain M, Petrylak DP, Sartor O, Higano CS, Dahut WL. A prospective analysis of the time to normalization of serum testosterone following 6 months of androgen deprivation therapy in patients on a randomized phase III clinical trial intermittent hormonal therapy. Presented at ASCO Annual Meeting, Chicago, May 2003.

69. Simons J, Higano C, Corman J, Hudes g, Centeno A, Dula E, Smith D, Steidle C, Sacks N, Small E. A phase II study of a high potency allogeneic GM-CSF gene-transduced prostate cancer cell line vaccine in patients with metastatic hormone-refractory prostate cancer. Presented at ASCO Annual Meeting, Chicago, May 2003.

70. Small EJ, Higano CS, Schellhammer PF, Rios I. Immunotherapy (APC8015, Provenge®) for androgen independent prostate cancer: final TTP and TDRP results and first survival data from a randomized placebo-controlled trial. Presented at 14th Annual Prostate Cancer Meeting, Vail, CO, February 2004.

71. Hussain A, Dipaola RS, Baron AD, Higano CS, Tchekmediyan NS, Miller J, Rothermel J. A phase IIa trial of weekly EPO906 in patients with hormone-refractory prostate cancer. *J Clin Oncol* 2004 23:396. Presented at ASCO Annual Meeting, New Orleans, May 2004.

72. Higano CS, Beer TM, Garzotto M, Ryan CW, Pitzel M, Works CR, Hall SP. Need for awareness and monitoring of ocular toxicities due to weekly docetaxel administration: experience during a trial of neoadjuvant docetaxel and mitoxantrone for patients with high-risk prostate cancer. *J Clin Oncol* 2004 23:399. Presented at ASCO Annual Meeting, New Orleans, May 2004.

73. Glode ML, Pantuck A, Higano CS, Meyer J, Hami L, Craig S, Berenson RJ, Frohlich MW. A phase I trial of CD3/CD28 activated T cells (Xcellerated T cells) in patients with hormone refractory prostate cancer. *J Clin Oncol* 2004 23:175 Presented at ASCO Annual Meeting, New Orleans, May 2004.

74. Small E, Higano CS, Smith D, Corman J, et al. A phase 2 sutdy of an allogeneic GM-CSF gene-transduced prostate cancer cell line vaccine in patients with metastatic hormone-refractory prostate cancer. *J Clin Oncol* 2004 23:396. Presented at ASCO Annual Meeting, New Orleans, May 2004.

75. Sartor O, Reid R, Higano C, Bushnell D, Quick D. Lack of significant toxicity following multi-dose samarium-153 lexidronom. Abstract 70. Presented at Prostate Cancer Foundation 11th Annual Scientific Retreat, 2004.

76. Aubin S, Higano CS. The combined treatment approach for men undergoing hormonal therapy for prostate cancer. *Urol Oncol* 2004 70, poster 92. Presented at 5th Annual SUO meeting, Bethesda, 2004.

77. Doshi RH, Lin DW, Higano CS, Ellis WJ, Lange PH. Exenterative salvage surgery for hormone refractory or radiation recurrent prostate cancer. *Urol Oncol* 2004 63, poster 78. Presented at 5th Annual SUO meeting, Bethesda, 2004.

78. Sartor O, Reid R, Higano C, Bushnell D, Quick D. Safety profile of repeated dose samarium 153 lexidronam in prostate cancer patients. *Urol Oncol* 2004 59, poster 70. Presented at 5th Annual SUO meeting, Bethesda, 2004.

79. Roudier MP, True LD, Higano CS, Ott SM, Vessella RL. Heterogeneous bone response to systemic therapy (bisphosphonates and/or chemotherapy) in patients with metastatic prostate cancer. *J Bone and Mineral Res* 2004 19:S122, #SA089.

80. O'Brien CA, Garzotto M, Higano CS, Wersinger EM, Kaimaktchiev V, Corless CL, Lange PH, True LD, Beer TM. Predictors of early relapse in high risk prostate cancer patients treated with neoadjuvant mitoxantrone and

docetaxel. *J Clin Oncol* 2005 23:412s. Presented at 41st Annual American Society of Clinical Oncology Meeting, Orlando, 2005.

81. Small EJ, Schellhammer PF, Higano CS, Neumanaitis J, Valone F, Herschberg RM. Results of a placebo-controlled phase III trial of immunotherapy with APC8015 for patients with hormone refractory prostate cancer. *J Clin Oncol* 2005 23:378s. Presented at 41st Annual American Society of Clinical Oncology Meeting, Orlando, 2005.

82. Smith M, Kabbinavar F, Saad F, Hussain A, Hei Y, Small E, Crook R, Higano C. Natural history of rising serum PSA in men with castrate nonmetastatic prostate cancer. *J Clin Oncol* 2005 23:381s. Presented at 41st Annual American Society of Clinical Oncology Meeting, Orlando, 2005.

83. Simons JW, Higano C, Smith D, Corman J, Steidle C, Gittelman M, Hudes G, Aimi J, Sacks N, Small E. Clinical and immunologic findings in a phase2 study of GM-CSF-secreting prostate cancer cell line vaccine in patients with metastatic hormone-refractory prostate cancer. *J Clin Oncol* 2005 23:170s. Presented at 41st Annual American Society of Clinical Oncology Meeting, Orlando, 2005.

84. Beer TM, Garzotto M, Lowe BA, Ryan CW, Rarick MU, Ellis WJ, Lange PH, Takayama T, Wersinger EM, Higano CS. Weekly docetaxel and mitoxantrone prior to prostatectomy in patients with high risk localized prostate cancer: results from 54 patients. Presented at 41st Annual American Society of Clinical Oncology Meeting, Orlando, 2005.

85. Sartor AO, Reid R, Higano C, Bushnell D, Quick D. Repeated dose samarium 153 lexidronam in patients with prostate cancer bone metastases. *J Clin Oncol* 2005 23:411s. Presented at 41st Annual American Society of Clinical Oncology Meeting, Orlando, 2005.

86. Howlander N, Tam S, Etzioni R, Higano CS. PSA doubling time during the "off-treatment" interval in men with biochemical relapse of prostate cancer treated with intermittent androgen suppression. *J Clin Oncol* 2005 23:420s. Presented at 41st Annual American Society of Clinical Oncology Meeting, Orlando, 2005.

87. Aubin S, Higano CS. Partners assessment of sexual function on androgren suppression (AS) for treatment of biochemical relapse of prostate cancer. *J Clin Oncol* 2005 23:793s. Presented at 41st Annual American Society of Clinical Oncology Meeting, Orlando, 2005.

88. Roudier MP, Coleman IM, True LD, Nelson PS, Ott SM, Higano CS, Vessella RL. Heterogeneity of bone formation and resorption in prostate cancer bone metastasis. Presented at 5th International Conference on Cancer-Induced Bone Disease, Davos, Switzerland, 2005.

89. Nelson PS, Huang A, True LD, Garzotto M, Wersinger EM, O'Brien CA, Ryan CW, Ellis WJ, Lange PH, Higano CS, Beer TM. Molecular correlates of prostate cancer response and resistance to neoadjuvant mitoxantrone and docetaxel. Presented at InterProstate SPORE Meeting, Houston, 2005.

90. Roudier MP, Morrissey C, Coleman LM, True LD, Higano CS, Nelson PS, Ott SM, Vessella RL. Bone formation and bone resorption in prostate cancer bone metastasis. Presented at ASBMR Annual Meeting, Nashville, 2005.

91. Higano CS, Burch PA, Small EJ, Schellhammer PF, Lemon R, Verjee SS, Hershberg RM. Immunotherapy (APC8015) for androgen independent prostate cancer: final progression and survival data from a second Phase 3 trial. *European J Cancer* Suppl. 2005 3(4):1 (abstract PS1). Presented at Annual ASCO Prostate Cancer Symposium, San Francisco, March 2006.

92. Jiang PY, Higano CS. Phase I study of interleukin 2 maintenance after induction with weekly docetaxel and estramustine in patients with metastatic hormone refractory prostate cancer. Presented at Annual ASCO Prostate Cancer Symposium, San Francisco, March 2006.

93. Cherrier MM, Montgomery RB, Nelson PS, Yu EY, Higano CS. Prospective measurements of mood and cognition in men undergoing androgen deprivation therapy (ADT for biochemical relapse of prostate cancer. Presented at Annual ASCO Prostate Cancer Symposium, San Francisco, March 2006.

94. Molife R, Patterson S, Riggs C, Higano CS, Stadler WM, Dearnaley D, Parker C, McCulloch W, Shalaurov A, de Bono J. Phase II study of FK228 (depsipeptide) in patients with metastatic hormone refractory prostate cancer. Presented at Annual ASCO Prostate Cancer Symposium, San Francisco, March 2006.

95. O'Brien CA, True LD, Higano CS, Garzotto M, Takayama T, Ellis WJ, Lange PH, Ryan CW, Beer TM. Histologic patterns seen in radical prostatectomy specimens of high-risk prostate cancer patients treated with neoadjuvant

chemotherapy are predictive of nodal metastases. Presented at Annual ASCO Prostate Cancer Symposium, San Francisco, March 2006.

96. Small EJ, Higano CS, Smith D, Corman J, Steidle C, Gittelman M, Hudes G, Sacks N, Simons, JW. Analysis of prognostic variables in phase II trials of GVAX vaccine for prostate cancer in metastatic hormone refractory prostate cancer. Presented at Annual ASCO Prostate Cancer Symposium, San Francisco, March 2006.

97. Beer TM, Higano CS. Darbepoetin administered every 4 weeks for anemia in advanced prostate cancer patients. Presented at 2006 ASCO Prostate Cancer Symposium, San Francisco, March 2006.

98. Cherrier M, Higano CS, Johnson M, Cross DJ, Minoshima S. Decreased cerebral metabolism from androgren suppression. Program No. 214.10. Presented at Society of Neuroscience Annual Meeting, Atlanta, June 2006.

99. Jiang P, Higano CS. Phase I study of interleukin 2 maintenance after induction with weekly docetaxel and estramustine in patients with metastatic hormone refractory prostate cancer. *J Clin Oncol*, 2006 ASCO Annual Meeting Proceedings Part 1, 2006 24:14526. Presented at ASCO Annual Meeting, Atlanta, June 2006.

100. Hussain M, Tangen CM, Schellhammer PF, Crawford ED, Higano CS, Wilding G, Akdas A, Small EJ, Donnelly B, Raghavan D. Absolute PSA value after androgen deprivation is a strong independent predictor of survival in new metastatic (D2) prostate cancer: data from Southwest Oncology Group Trial 9346 (INT-0162). *J Clin Oncol*, 2006 ASCO Annual Meeting Proceedings Part 1, 2006 24:4517. Presented at ASCO Annual Meeting, Atlanta, June 2006.

101. Molife R, Patterson S, Riggs C, Higano CS, Stadler WM, Dearnaley D, Parker C, McCulloch W, Shalaurov A, De-Bono J. Phase II study of FK228 in patients with hormone refractory prostate cancer. *J Clin Oncol*, 2006 ASCO Annual Meeting Proceedings Part 1, 2006 24:14554. Presented at ASCO Annual Meeting, Atlanta, June 2006.

102. Small E, Higano CS, Tchekmedyian N, Sartor O, Stein B, Young R, Vestal J, Moseley W, Fischkoff S, Lowy I. Randomized phase II study comparing 4 monthly does of ipilimumab (MDX-101) as a single agent or in combination with a single dose of docetaxel in patients with hormone-refractory prostate cancer. *J Clin Oncol*, 2006 ASCO Annual Meeting Proceedings Part 1, 2006 24:4609. Presented at ASCO Annual Meeting, Atlanta, June 2006.

103. Higano CS, True LD, Roudier MP, Lange PH, Vessella RL. History of the University of Washington Tissue Acquisition at Necropsy Program in Prostate Cancer. Presented at 14th SPORE Investigators' Workshop, Baltimore, July 2006.

104. Higano CS, Gordon M, LoRusso P, Fox F, Katz T, Roecker J, Rowinsky E, Youssefian H. A phase I, first in man study of weekly IMC-A12, a fully human insulin like growth factor-I receptor IgG1 monoclonal antibody, in patients with advanced solid tumors. Presented at 18th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics; *Eur J Cancer* Suppl 4(12):195, Prague, November 2006.

105. Higano CS, Yu EY, Whiting SH, Gordon M, LoRusso P, Fox F, Katz T, Roecker J, Rowinsky E, Schwartz J. A phase I, first in man study of weekly IMC-A12, a fully human insulin like growth factor-I receptor IgG1 monoclonal antibody, in patients with advanced solid tumors. Presented at Annual ASCO Prostate Cancer Symposium, Orlando, February 2007.

106. Yu EY, Hackenbracht JA, Muzi M, Link M, Eary JF, Higano CS, Montgomery RB, Mankoff DA. Positron Emission Tomography measures response of prostate cancer bone metastases to therapy. Presented at Annual ASCO Prostate Cancer Symposium, Orlando, February 2007.

107. Montgomery RB, Mostaghel E, Vessella R, Hess D, True L, Plymate S, Higano C, Lange P, Nelson P. Androgen synthesis in castration-adapted metastatic prostate cancer. Presented at Annual ASCO Prostate Cancer Symposium, Orlando, February 2007.

108. Scher HI, Halabi S, Tannock I, Morris M, Higano C, Beer T, Sternberg C, Eisenberger M, Martin A, Hussain M. The Prostate Cancer Clinical Trials Working Group consensus for phase II trials in metastatic castration-resistant prostate cancer. Presented at Annual ASCO Prostate Cancer Symposium, Orlando, February 2007.

109. Sim H, Lin DW, Higano CS, Ellis WJ, Lange PH. Exenterative salvage surgery for hormone refractory prostate cancer. Presented at Annual ASCO Prostate Symposium, Orlando, February 2007.

110. Roudier M, Morrissey C, Huang L, Rohrbach K, Keller E, True L, Higano C, Vessella R, Dougall W. Immunohistochemical detection in post-mortem specimens of RANK/RANKL/OPG in prostate cancer bone and soft tissue metastases. Presented at Annual ASCO Prostate Cancer Symposium, Orlando, February 2007.

111. Higano CS, Yu EY, Whiting SH, Gordon M, LoRusso P, Fox F, Katz T, Roecker J, Schwartz JD. A phase I, first in man study of weekly IMC-A12, a fully human insulin like growth factor-I receptor IgG1 monoclonal antibody, in patients with advanced solid tumors. *J Clin Oncol* 2007 ASCO Annual Meeting Proceedings Part I. 25(18S):3505. Presented at ASCO Annual Meeting, Chicago, June 2007.

112. Telesca D, Higano CS, Yu EY, Montgomery RB, Tam S, Russell KJ, Nelson PS, Etzioni RB. Duration of the first off treatment period is associated with time to androgen independence and survival in men with localized or biochemical relapse of prostate cancer treated on prospective trial of intermittent androgen deprivation. *J Clin Oncol* 2007 ASCO Annual Meeting Proceedings Part I. 25(18S):5146. Presented at ASCO Annual Meeting, Chicago, June 2007.

113. Scher H, Halabi S, Tannock I, Morris M, Higano C, Kelly WK, Sternberg C, Eisenberger M, Martin A, Hussain M, for the PSAWG. The Prostate Cancer Clinical Trials Working Group consensus criteria for phase II clinical trials for castration-resistant prostate cancer. *J Clin Oncol* 2007 ASCO Annual Meeting Proceedings Part I. 25(18S):5057. Presented at ASCO Annual Meeting, Chicago, June 2007.

114. Parker C, Molife R, Karavasilis V, Reid A, Patterson G, Riggs C, Higano C, Stadler WM, McCulloch W, de Bono JS. Romidepsin (FK228), a histone deacetylase inhibitor: final results of a phase II study in metastatic hormone refractory prostate cancer *J Clin Oncol* 2007 ASCO Annual Meeting Proceedings Part I. 25(18S):15507. Presented at ASCO Annual Meeting, Chicago, June 2007.

115. Cherrier M, Higano CS, Johnson M, Cross DJ, Minoshima S. Decreased cerebral metabolism from androgren suppression. Presented at IMPaCT: Innovative Minds in Prostate Cancer Today, Atlanta, September 2007.

116. Higano CS, LoRusso P, Gordon M, Yu EY, Whiting SH, Fox F, Katz T, Rowinsky E, Youssoufian H. A phase I study of the recombinant human IgG1 anti-IGF-IR monoclonal antibody IMC-A12, administered on a weekly basis to patients with advanced solid tumors: interim analysis. Presented at 19th AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, San Francisco, October 2007.

117. Aragon-Ching JB, Gulley JL, Steinberg SM, Hussain MH, Sartor O, Higano CS, Petrylak D, Chatta GS, Arlen PM, Figg WD, Dahut WL. Kinetics of serum androgen normalization after limited androgen deprivation therapy in non-metastatic prostate cancer. *J Urol.* 2008 Oct;180(4):1432-1437. Presented at Society of Urologic Oncology Meeting, Bethesda, November 2007.

118. Mostaghel EA, Montgomery RB, Vessella R, Kalhorn T, True L, Higano C, Nelson PS. Correlating androgen levels and steroidogenic enzyme expression in castration resistant prostate cancer metastases. Presented at Annual ASCO Genitourinary Symposium, San Francisco, February 2008.

119. Aragon-Ching JB, Gulley JL, Steinberg SM, Hussain MH, Sartor O, Higano C, Petrylak D, Chatta GS, Arlen PM, Figg WD, Dahut WL. Kinetics of serum androgen normalization after limited androgen deprivation therapy in non-metastatic prostate cancer. Presented at Annual ASCO Genitourinary Symposium, San Francisco, February 2008.

120. Higano CS, Yu EY, Whiting SH, Gordon MS, LoRusso P, Fox F, Katz TL, Rowinsky E, Schwartz JD. A phase I, first in man study of weekly IMC-A12, a fully human insulin like growth factor-I receptor IgG1 monoclonal antibody, in patients with advanced solid tumors. Presented at Annual ASCO Genitourinary Symposium, San Francisco, February 2008.

121. Goldman B, Hussain M, Tangen C, Higano C, Petrylak D, Vogelzang N, Crawford E. Prostate-specific antigen predicts overall survival in patients with metastatic prostate cancer: data from S9346 and S9916. Presented at Annual ASCO Genitourinary Symposium, San Francisco, February 2008.

122. Scher HI, Beer T, Higano C, Danila DC, Shelkey J, Hirmand M, Hung D, Morris M, Larson SM, Sawyers C. Phase I/II study of the androgren receptor antagonist MDV3100 in castration-resistant prostate cancer. AACR meeting abstracts 2008:LB-203. Presented at American Association for Cancer Research Annual Meeting, San Diego, April 2008.

123. Beer TM, Slovin SF, Higano CS, Tejwani S, Dorff T, Stakevich E, Lowy I, Prostate Cancer Clinical Trials Consortium. Phase I trial of ipilimumab (IPI) alone and in combination with radiotherapy (XRT) in patients with metastatic castration resistant prostate cancer. *J Clin Oncol* 26:2008 (May 20 suppl; abstr 5004). Presented at ASCO Annual Meeting, Chicago, June 2008.

124. Gulati R, Yu EY, Telesca D, Jiang P, Montgomery RB, Tam S, Russell KJ, Nelson PS, Etzioni RB, Higano CS. Testosterone kinetics in the first cycle of intermittent androgen deprivation for men with localized or biochemical relapse of

prostate cancer. *J Clin Oncol* 26:2008 (May 20 suppl; abstr 5134). Presented at ASCO Annual Meeting, Chicago, June 2008.

125. Scher HI, Beer T, Higano C, Danila D, Montgomery B, Shelkey J, Hirmand M, Hung D, Sawyers C. Phase I/II study of MDV3100 in patients with progressive castration-resistant prostate cancer. *J Clin Oncol* 26:2008 (May 20 suppl; abstr 5006). Presented at ASCO Annual Meeting, Chicago, June 2008.

126. Hussain M, Goldman, Tangen C, Higano C, Petrylak DP, Crawford ED. Use of prostate-specific antigen progression to predict overall survival in patients with metastatic prostate cancer: data from S9346 and S9916. *J Clin Oncol* 26:2008 (May 20 suppl; abstr 5015). Presented at ASCO Annual Meeting, Chicago, June 2008.

127. Figg WD, Aragon-Ching JB, Steinberg SM, Gulley JL, Arlen PM, Sartor O, Petrylak DP, Higano CS, Hussain MH, Dahut WL. Randomized phase III trial of thalidomide or placebo for non-metastatic PSA recurrent prostate cancer treated with intermittent therapy. *J Clin Oncol* 26:2008 (May 20 suppl; abstr 5016). Presented at ASCO Annual Meeting, Chicago, June 2008.

128. Cherrier MM, Green P, Schellenberg GS, Higano CS. Association of apolipoprotein E on serum abeta levels in men undergoing intermittent androgen ablation. Presented at Alzheimer's Association International Conference on Alzheimer's Disease, Chicago, June 2008.

129. Smith D, Small E, Corman J, Higano C, Nguyen M, Harding T, Jooss K, Chondros D. Analysis of factors influencing survival in patients with metastatic hormone-refractory prostate cancer following GVAX immunotherapy for prostate cancer. Presented at National Cancer Research Institute Conference, Birmingham, UK, October 2008.

130. Mostaghel EA, Montgomery RB, Vessella R, Kalhorn TF, True LD, Higano C, Nelson PS. Androgen levels and steroidgenic enzyme expression in castration resistant prostate cancer metastases. Presented at: Prostate Cancer Foundation Annual Scientific Retreat, Lake Tahoe, October 2008.

131. Rothenberg ML, Poplin E, Mehnert J, LoRusso P, Fox F, Schwartz J, Rowinsky E, Higano C. Pharmacokinetic and pharmacodynamic results of phase 1 studies of IMC-A12, a recombinant human insulin-like growth factor-I receptor IgG_1 monoclonal antibody, in patients with advanced solid malignancies. Presented at 20th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics, Geneva, October 2008.

132. Scher HI, Beer T, Higano CS, Efstathiou E, Shelky J, Hirmand M, Hung D, Anand A, Larson S, Fleisher Sawyers CL. Phase 1-2 study of MDV3100 in castration-resistant prostate cancer. Presented at Annual ASCO Genitourinary Cancers Symposium, Orlando, February 2009.

133. Higano C, Saad F, Somer B, Curti B, Petrylak D, Drake CG, Schnell F, Redfern CH, Schrijvers D, Sacks N. A phase 3 trial of GVAX immunotherapy for prostate cancer vs. docetaxel plus prednisone in asymptomatic, castration-resistant prostate cancer. Presented at Annual ASCO Genitourinary Cancers Symposium, Orlando, February 2009.

134. Scher HI, Beer T, Higano C, Efstathiou E, Anand A, Hirmand M, Hung D, Larson S, Fleisher M, Sawyers C. Clinical study of MDV3100 in progressive castration-resistant prostate cancer. *J Urol* 181(4 Suppl):230 abstract 641. Presented at American Urological Society Annual Meeting, Chicago, April 2009.

135. Schellhammer PF, Higano C, Berger ER, Shore N, Small E, Penson D, Ferrari A, Sims R, Yuh L, Frohlich M, Kantoff P, IMPACT Study Investigators. A randomized, double-blind, placebo-controlled, multi-center, phase III trial of sipuleucel-T in men with metastatic, androgen independent prostatic adenocarcinoma. Presented at American Urological Society Annual Meeting, Chicago, April 2009.

136. Rademacher BL, Garzotto M, Higano CS, O'Brien CA, Janeba N, Fazli L, Lange PH, Lieberman S, Beer TM. Five-year relapse-free survival and predictors of relapse following pre-operative docetaxel and mitoxantrone for high-risk localized prostate cancer. *J Clin Oncol* 27:15s, 2009 (suppl; abstr 5121). Presented at ASCO Annual Meeting, Orlando, May 2009.

137. Higano CS, Alumkal J, Ryan CJ, Yu EY, Beer TM, Chandrawansa K, Katz T, Youssoufian H, Schwartz J, Prostate Cancer Clinical Trials Consortium. A phase 2 study evaluating the efficacy and safety of single agent IMC A12, a monoclonal antibody against the insulin-like growth factor-I receptor, as monotherapy in patients with metastatic, asymptomatic castrate resistant prostate cancer. *J Clin Oncol* 27:15s, 2009 (suppl; abstr 5142). Presented at ASCO Annual Meeting, Orlando, May 2009.

138. Scher HI, Beer TM, Higano CS, Taplin M, Efstathiou E, Anand A, Hung D, Hirmand M, Fleisher M, The Prostate Cancer Clinical Trials Consortium. Anitumor activity of MDV3100 in a Phase 1-2 study of castration-resistant prostate cancer. *J Clin Oncol* 27:15s, 2009 (suppl; abstr 5011). Presented at ASCO Annual Meeting, Orlando, May 2009.

139. Slovin SF, Beer TM, Higano CS, Tejwani S, Hamid O, Picus J, Harzstark A, Scher HI, Lan Z, Lowy I. Prostate Cancer Clinical Trials Consortium. Initial phase II experience of ipilimunab alone and in combination with radiotherapy in patients with metastatic castration resistant prostate cancer. *J Clin Oncol* 27:15s, 2009 (suppl; abstr 5138). Presented at ASCO Annual Meeting, Orlando, May 2009.

140. Hotte SJ, Yu EY, Hirte HW, Higano CS, Gleave M, Chi KN. OGX-427, a 2'methoxyethyl antisense oligonucleotide against HSP27: results of a first-in human trial. *J Clin Oncol* 27:15s, 2009 (suppl; abstr 3506). Oral presentation at ASCO Annual Meeting, Orlando, May 2009.

141. Vinson J, Mathew P, Beer T, Carducci M, Oh W, Small E, Wilding G, Higano C, Hussain M, Scher HI, Prostate Cancer Clinical Trials Consortium. Prostate cancer clinical trials consortium: a multi-center mechanism for the rapid design development, and implementation of early phase clinical trials. *J Clin Oncol* 27, 2009 (suppl; abstr e16065). Presented at ASCO Annual Meeting, Orlando, May 2009.

142. Schellhammer PF, Higano CS, Berger ER, Shore ND, Small EJ, Penson DF, Sims RB, Yuh L, Frohlich MW, Kantoff PW, for the IMPACT Study Investigators. A randomized, double-blind, placebo-controlled, multi-center, phase III trial of sipuleucel-T in men with metastatic, androgen independent prostatic adenocarcinoma. Presented at ASCO Annual Meeting, Orlando, May 2009.

143. Hussain M, Tangen CM, Eisenberger MA, Higano CS, Small EJ, Wilding G, Donnelly BJ, McLeod D, Crawford ED, Thompson IM. Improved overall survival of patients with new metastatic prostate cancer: better or stage migration? Data from SWOG S9346 and 8894. Presented at Annual ASCO Genitourinary Cancers Symposium, San Francisco, March 2010.

144. Kantoff PW, Higano C, Berger ER, Shore N, Small E, Penson D, Sims R, Xu Y, Frohlich MW, Schellhammer PF for the IMPACT Study Investigators. Updated survival results of the IMPACT trial of sipuleucel-t for metastatic castration resistant prostate cancer. Presented at Annual ASCO Genitourinary Cancers Symposium, San Francisco, March 2010.

145. Higano CS, Alumkal JJ, Ryan CJ, Yu EY, Beer TM, Fox FE, Dontabhaktuni A, Youssoufian H, Schwartz JD. A phase 2 study of cixutumumab (IMC-A12), a monoclonal antibody against the insulin-like growth factor-I receptor, monotherapy in metastatic castrate resistant prostate cancer: feasibility of every 3 week dosing and updated results of every 2 week dosing. Presented at Annual ASCO Genitourinary Cancers Symposium, San Francisco, March 2010.

146. Scher HI, Anand A, Beer TM, Higano CS, Danila DC, Hirmand M, Larson SM, Sawyers CL, Fleisher M, Heller G. Circulating tumor cells (CTC) and prostate-specific antigen (PSA) as response indicator biomarkers in patients with progressive castration-resistant prostate cancer (CRPC) treated with MDV3100: toward the development of a biomarker basket. Presented at Annual ASCO Genitourinary Cancers Symposium, San Francisco, March 2010.

147. Small EJ, Beer TM, Weinberg VK, Higano CS, Alumkal JJ, Yu EY, Nordquist LT, Rosenberg JE, Sun J, Lin AM. Intermittent chemotherapy (ICh) for metastatic castration-resistant prostate cancer (mCRPC): Results of a prospective randomized phase II trial of the Department of Defense Prostate Cancer Clinical Trials Consotium. Presented at ASCO Genitourinary Cancers Symposium, San Francisco, CA, March 2010.

148. Scher HI, Beer TM, Higano CS, Logothetis C, Taplin ME, Efstathious E, Hirmand M. Antitumor Activity of MDV3100 in a Phase 1-2 Study of Advanced Prostate Cancer. *J Urol.* April 2010; 183(4):e2627-e228. Presented at American Urological Association Annual Meeting, San Francisco, May 2010.

149. Hall AJ, Schellhammer PF, Higano CS, Corman JM, Beer TM, Small EJ, Pantuck AJ, Kassabian VS, Stewart FP, Sims RB. Integrated Safety Results from four randomized, double-blind, placebo-controlled studies of sipuleucel-T. *J Urol.* April 2010; 183(4):e263. Presented at American Urological Association Annual Meeting, San Francisco, May 2010.

150. Hotte SJ, Yu EY, Hirte HW, Higano CS, Gleave ME, Chi KN. Phase I trial of OGX-427, a 2'methoxyethyl antisense oligonucleotide (ASO), against heat shock protein 27 (Hsp27): final results. *J Clin Oncol* 28:15s, 2010 (suppl; abstr 3077). Presented at ASCO Annual Meeting, Chicago, June 2010.

151. Anand A, Scher HI, Beer TM, Higano CS, Danila DC, Taplin M, Efstathiou E, Hirmand M, Sawyers CL, Heller G. Circulating tumor cells (CTC) and prostate specific antigen (PSA) as response indicator biomarkers in chemotherapy-

naïve patients with progressive castration-resistant prostate cancer (CRPC) treated with MDV3100. *J Clin Oncol.* 28:15s, 2010 (suppl; abstr 4546). Presented at ASCO Annual Meeting, Chicago, June 2010.

152. Beer TM, Rademacher BL, Geng H, Pittsenbarger J, Grzotto M, Nelson P, Higano CS, Qian DZ. Effect of ID1 expression change following chemotherapy on chemotherapy sensitivity. *J Clin Oncol* 28:15s, 2010 (suppl; abstr 4548). Presented at ASCO Annual Meeting, Chicago, June 2010.

153. Higano CS, Small EJ, Schellhammer PF, Kantoff P, Redfern CH, Nemunaitis JJ, Nabhan C, Xu Y, Whitmore JB, Frohlich MW. Predictors of outcome and subgroup results from the integrated analysis of sipuleucel-T trials in metastatic castration-resistent prostate cancer. *J Clin Oncol.* 2010, 28:7s. Presented at ASCO Annual Meeting, Chicago, June 2010.

154. Yu EY, Kuo K, Gulati R, Jiang PY, Higano CS. Dynamics of bone mineral density during intermittent androgen deprivation for men with biochemical recurrence of prostate cancer. *J Clin Oncol* 28:15s, 2010 (suppl; abstr 4558). Presented at ASCO Annual Meeting, Chicago, June 2010.

155. Monique Cherrier, Celestia Higano, Tom Erickson, Carol Moinpour, Maria Holsman, Brenda Kurland. Mood Changes in Men Undergoing Intermittent Androgen Deprivation Therapy for Prostate Cancer. Abstract #3388. Presented at the 5th Annual Biennial Cancer Survivorship Research Conference, Washington DC, June 2010.

156. Klotz L, O'Callaghan CJ, Ding K, Dearnaley DP, Higano CS, Horwitz EM, Malone S, Goldenberg SL, Gospodarowicz MK, Crook JM. A phase III randomized trial of intermittent versus continuous androgen suppression for PSA progression after radical therapy (NCIC CTG PR.7/SWOG JPR.7/CTSU JPR.7/UK Intercontinental Trial CRUKE/01/013). *J Clin Oncol* 29:2011 (suppl 7, abstr 3). Presented at Annual ASCO Genitourinary Cancers Symposium, Orlando, February 2011.

157. Yu EY, Nathan FE, Higano CS. Role of detection of metastatic disease as a leading cause of screening failure in an ongoing phase III trial of zibotentan versus placebo in patients with non-metastatic castration-resistant prostate cancer (CRPC). *J Clin Oncol* 29: 2011 (suppl 7; abstr 135). Presented at Annual ASCO Genitourinary Cancers Symposium, Orlando, February 2011.

158. Harzstark AL, Beer TM, Weinberg VK, Higano CS, Nordquist LT, Rosenberg JE, Alumkal JJ, Yu EY, Mi J, Small EJ. Intermittent chemotherapy (Ich) for metastatic castration-resistant prostate cancer (mCRPC): results of a prospective randomized phase II trial of the DoD prostate cancer clinical trials consortium. *J Clin Oncol* 29: 2011 (suppl 7; abstr 133). Presented at Annual ASCO Genitourinary Cancers Symposium, Orlando, February 2011.

159. Nelson JB, Fizazi K, Miller K, Higano CS, Moul JW, Morris T, McIntosh S, Pemberton K, Gleave ME. Phase III Study of the Efficacy and Safety of Zibotentan (ZD4054) in Patients With Bone Metastatic Castration-Resistant Prostate Cancer (CRPC). *J Clin Oncol* 29: 2011 (suppl 7; abstr 117). Presented at Annual ASCO Genitourinary Cancers Symposium, Orlando, February 2011.

160. Higano CS, Beer TM, Taplin ME, Efstathious E, Anand A, Hirmand M, Fleisher M, Scher HI, Prostate Cancer Clinical Trials Consortium. Antitumor Activity of MDV3100 in pre- and post-docetaxel advanced prostate cancer: Long-term follow-up of a Phase 1-2 Study. *J Clin Oncol* 29: 2011 (suppl 7; abstr 134). Presented at Annual ASCO Genitourinary Cancers Symposium, Orlando, February 2011.

161. Hussain M, Rathkopf D, Liu G, Armstrong A, Kelly WK, Ferrari A, Hainsworth J, Yang L, Schwartz J, Youssougian H, Higano CS. A phase 2 randomized study of cixutumumab (IMC-A12) or ramucirumab (IMC-1121B) plus mitoxantrone and prednisone in patients (pts) with metastatic castration resistant prostate cancer (CRPC) following disease progression on docetaxel-based chemotherapy. Presented at DOD IMPaCT Conference, Orlando, March 2011.

162. Higano CS, Beer TM, Yu EY, Taplin M, Efstathiou E, Anand A, Hirmand M, Fleisher M, Scher H. Prostate Cancer Clinical Trials Consortium. Long-term efficacy results from the phase 1-2 study of MDV3100 in pre- and post-docetaxel prostate cancer. Presented at 26th Annual Congress of the European Association of Urology, Vienna, March 2011.

163. Nguyen HM, Corey E, Morrissey C, Nelson PS, Zhang X, Plymate SR, Higano CS, Lange PH, Roudier MP, True LD, Vessella RL. The biological and molecular characterization of 24 unique prostate cancer xenograft lines, including responses to therapy. *Cancer Res* February 6, 2012 72; C34. Presented at AACR 102nd Annual Meeting, Orlando, April 2011.

164. Higano CS, Beer TM, Yu EY, Taplin M, Efstathiou E, Anand A, Hirmand M, Fleisher M, Sher H. 647 phase 1-2 study of MDV3100 in pre- and post-docetaxel advanced prostate cancer: long-term efficacy results. *J Urol.* 2011 April; 185(4s): e262. Presented at American Urological Association Annual Meeting, Washington, May 2011.

165. Chi KN, De Bono JS, Higano CS. SYNERGY: A randomized phase III study comparing first-line docetaxel/prednisone to docetaxel/prednisone plus custirsen in metastatic castrate-resistant prostate cancer (mCRPC). *J Clin Oncol* 29: 2011 (suppl; abstr TPS180). Presented at ASCO Annual Meeting, Chicago, June 2011.

166. Crook JM, O'Callaghan CJ, Ding K, Duncan G, Dearnaley DP, Higano CS, Horwitz EM, Frymire E, Malone S, Chin J, Nabid A, Warde PR, Corbett TB, Angyalfi S, Goldenberg SL, Gospodarowicz MK, Saad F, Logue JP, Schellhammer PF, Klotz L. A phase III randomized trial of intermittent versus continuous androgen suppression for PSA progression after radical therapy (NCIC CTG PR.7/SWOG JPR.7/CTSU JPR.7/ UK Intercontinental Trial CRUKE/01/013). *J Clin Oncol* 29: 2011 (suppl; abstr 4514). Presented at ASCO Annual Meeting, Chicago, June 2011.

167. Small EJ, Higano CS, Kantoff PW, Whitmore JB, Frohlich MW, Petrylak DP. Time to disease-related pain after sipuleucel-T in asymptomatic patients with metastatic castrate-resistant prostate cancer (mCRPC): Results from three randomized phase III trials. *J Clin Oncol* 29: 2011 (suppl; abstr 4661). Presented at ASCO Annual Meeting, Chicago, June 2011.

168. Yu EY, Nathan FE, Higano CS. Detection of metastatic disease as a leading cause of screening failure in a phase III trial of zibotentan versus placebo in patients with nonmetastatic castration-resistant prostate cancer (CRPC). *J Clin Oncol* 29: 2011 (suppl; abstr 4655). Presented at ASCO Annual Meeting, Chicago, June 2011.

169. Small E, Higano CS, Kantoff P, Whitmore J, Frohlich M, Petrylak D. Time to disease-related pain after sipuleucel-T in asymptomatic patients with metastatic castrate resistant prostate cancer (mCRPC): results from 3 randomized phase III trials. *J Clin Oncol* 29: 2011 (suppl; abstr 4661). Presented at The European Multidisciplinary Cancer Congress, Stockholm, September 2011.

170. Higano CS, Beer, TM, Yu EY, Taplin M, Efstathiou E, Anand A, Hirmand M, Fleisher M, Scher HI, and The Prostate Cancer Clinical Trials Consortium. Long-term efficacy results from the phase 1-2 study of MDV3100 in pre- and post-docetaxel advanced prostate cancer. Presented at 3rd European Multidisciplinary Meeting on Urological Cancers, Barcelona, November 2011.

171. Hussain M, Rathkopf DE, Liu G, Armstrong AJ, Kelly WK, Ferrari AC, Hainsworth JD, Yang L, Schwartz JD, Higano CS. A phase II randomized study of cixutumumab (IMC-A12: CIX) or ramucirumab (IMC-1121B: RAM) plus mitoxantrone (M) and prednisone (P) in patients (pts) with metastatic castrate-resistant prostate cancer (mCRPC) following disease progression (PD) on docetaxel (DCT) therapy. *J Clin Oncol* 30, 2012 (suppl 5; abstr 97). Presented at Annual ASCO Genitourinary Cancers Symposium, San Francisco, February 2012.

172. Yu EY, Kuo, KF, Hunter-Merrill R, Gulati R, Hall SP, Gambol TE, Etzioni RD, Higano CS. Relationship of time to testosterone (T) and PSA rises during the first "off treatment" interval (1OFF) of intermittent androgen deprivation (IAD) with time to castration resistance (CRPC) and prostate cancer mortality (PCM) in men with biochemical relapse (BR). *J Clin Oncol* 30, 2012 (suppl 5; abstr 99). Presented at Annual ASCO Genitourinary Cancers Symposium, San Francisco, February 2012.

173. Small EJ, Weinberg VK, Ryan CJ, Higano CS, Lin AM, Maruca Y, Alumkal JJ, Yu EY, Rosenberg JE, Beer TM. A prospective randomized phase II trial evaluating maintenance GM-CSF in an intermittent chemotherapy (chemo) regimen for metastatic castration-resistant prostate cancer (mCRPC): A DoD prostate cancer clinical trials consortium trial. *J Clin Oncol* 30, 2012 (suppl 5; abstr 35). Presented at Annual ASCO Genitourinary Cancers Symposium, San Francisco, February 2012.

174. Slovin SF, Hamid O, Tejwani S, Higano CS, Harzstark A, Alumkal JJ, Scher HI, Chin KM, Gagnier P, McHenry MB, Beer T. Ipilimumab (IPI) in metastatic castrate-resistant prostate cancer (mCRPC): results from an open-label, multicenter phase I/II study. *J Clin Oncol* 30, 2012 (suppl 5; abstr 25). Presented at Annual ASCO Genitourinary Cancers Symposium, San Francisco, February 2012.

175. Sheikh NA, Small EJ, Quinn DI, Higano CS, Lin DW, Wesley JD, Haynes H, Stewart FP, Poehlein DH, Trager JB. Sipuleucel-T product characterization across different disease states of prostate cancer. *J Clin Oncol* 30, 2012 (suppl 5; abstr 42). Presented at Annual ASCO Genitourinary Cancers Symposium, San Francisco, February 2012.

176. Small E, Higano CS, Kantoff P, Whitmore J, Frohlich M, Petrylak D. Time to disease-related pain after sipuleucel-T in asymptomatic patients with metastatic castrate resistant prostate cancer (mCRPC): integrated results from 3 randomized phase III trials. *J Clin Oncol* 29: 2011 (suppl; abstr 4661). Poster presented at 27th Annual European Association of Urology Congress Paris, February 2012.

177. Zhang X, Larson S, Dumpit R, Coleman I, Lakely B, Roudier M, Higano CS, True LD, Lange PH, Nelson PS, Corey E, Vessella RL, Morrissey C. The identification of osteoblastic factors in prostate cancer bone metastases. Presented at Annual AACR Meeting, Chicago, February 2012.

178. Tattersall A, Cherrier M, Church A, Andersen K, Higano C, Moinpour C, Kurland B, Chai S. Companion ratings of emotions, quality of life, and cognitive functioning in prostate cancer patients undergoing androgen deprivation therapy. The view from the other side. Presented at International Cognition and Cancer Taskforce, Paris, March 2012.

179. Fearn PA, Higano CS, Gore JL, Masys DR, Tarczy-Hornoch P. A hybrid system using CAISIS and REDCap for comprehensive management of longitudinal follow-up and patient-reported outcomes. Presented at AMIA Joint Summits on Translational Science, San Francisco, March 2012.

180. Hirata Y, Akakura K, Higano CS, Bruchovsky N, Aihara K. Mathematically modeling prostate cancer under intermittent androgen suppression: towards robust scheduling. Presented at 2nd International Symposium on Innovative Mathematical Modelling, Tokyo, May 2012.

181. Hussain M, Tangen CM, Higano CS, Crawford ED, Liu G, Wilding G, Prescott S, Akdas A, Small EJ, Dawson NA, Donnelly BJ, Venner P, Vaishampayan UN, Schellhammer PF, Quinn DI, Raghaven D, Vogelzang NJ, Thompson IM. Intermittent (IAD) versus continuous androgen deprivation (CAD) in hormone sensitive metastatic prostate cancer (HSM1PC) patients (pts): Results of S9346 (INT-0162), an international phase III trial. *J Clin Oncol* 30, 2012 (suppl; abstr 4). Presented at ASCO Annual Meeting, Chicago, June 2012.

182. Goldkorn A, Ely B, Quinn DI, Tangen CM, Tai Y-C, Twardowski PW, Van Veldhuizen PJ, Agarwal N, Carducci M, Monk JP, Garzotto MG, Mack PC, Lara PN, Higano CS, Hussain MH, Vogelzang NJ, Cote RJ, Thompson IM, Southwest Oncology Group. Results of telomerase activity measurements from live circulating tumor cells captured on a slot microfilter in a phase III SWOG-coordinated prostate cancer trial (S0421). *J Clin Oncol* 30, 2012 (suppl; abstr 4663). Presented at ASCO Annual Meeting, Chicago, June 2012.

183. Vogelzang NJ, Ely B, Fink LM, Goldkorn A, Tangen CM, Twardowski PW, Van Veldhuizen PJ, Agarwal N, Carducci M, Monk JP, Garzotto MG, Lara PN, Mack PC, Higano CS, Hussain MH, Quinn DI, Cote RJ, Thompson IM. Circulating Tumor Cell Counts (CTC) as prognostic of overall survival (OS) in SWOG S0421-docetaxel with or without atrasentan for metastatic castration resistant prostate cancer (mCRPC). *J Clin Oncol* 30, 2012 (suppl; abstr 10503). Presented at ASCO Annual Meeting, Chicago, June 2012.

184. Moinpour C, Berry DL, Ely B, Tangen CM, Higano CS, Picus J, Schellhammer PF, Skinner EC, Cher ML, Thompson IM, Hussain MH. Preliminary quality of life outcomes for SWOG-9346: Intermittent androgen deprivation in patients with hormone sensitive metastatic prostate cancer (HSM1PC)--phase III. *J Clin Oncol* 30, 2012 (suppl; abstr 4571). Presented at ASCO Annual Meeting, Chicago, June 2012.

185. Quinn DI, Sheikh NA, Higano CS, Wesley JD, Haynes H, Stewart FP, Poehlein CH, Trager JB. Sipuleucel-T product characterization across different disease states of prostate cancer. *J Clin Oncol* 30, 2012 (suppl 5; abstr 42) Poster presented at ASCO Annual Meeting, Chicago, June 2012.

186. Yu EY, Kuo KF, Hunter-Merrill R, Gulati R, Hall SP, Gambol TE, Etzioni RD, Higano CS. Time to testosterone (T) and PSA rises during first "off treatment" interval (1OFF-2ON) of intermittent androgen deprivation (IAD) as prognostic for time to castration resistance (CRPC) and prostate cancer mortality (PCM) in men with biochemical relapse (BR). *J Clin Oncol* 30, 2012 (suppl; abstr 4557). Presented at ASCO Annual Meeting, Chicago, June 2012.

187. Smith M, Sweeney C, Rathkopf DE, Scher HI, Logothetis C, George DJ, Higano CS, Yu EY, Harzstark AL, Small EJ, Sartor O, Gordon MS, Vogelzang NJ, Smith DC, Hussain MH, deBono JS, Haas NB, Scheffold C, Lee Y, Corn PG. Cabozantinib (XL184) in chemotherapy-pretreated metastatic castration resistant prostate cancer (mCRPC): Results from a phase II nonrandomized expansion cohort (NRE). *J Clin Oncol* 30, 2012 (suppl; abstr 4513). Oral presentation at ASCO Annual Meeting, Chicago, June 2012.

188. Quinn DI, Tangen CM, Hussain MH, Lara PN, Goldkorn A, Garzotto MG, Mack PC, Carducci M, Monk JP, Twardowski PW, Van Veldhuizen PJ, Agarwal N, Higano CS, Vogelzang NJ, Thompson IM. SWOG S0421: Phase III study of docetaxel (D) and atrasentan (A) versus docetaxel and placebo (P) for men with advanced castrate resistant prostate cancer (CRPC). *J Clin Oncol* 30, 2012 (suppl; abstr 4511). Presented at ASCO Annual Meeting, Chicago, June 2012.

189. Higano CS, Hirata Y, Akakura K, Bruchovsky N, Aihara K. Retrospective mathematical analysis of serial prostate specific antigen (PSA) measurements for patients with M0 prostate cancer treated with intermittent androgen suppression (IAS). *J Clin Oncol* 30, 2012 (suppl; abstr e15201). Presented at ASCO Annual Meeting, Chicago, June 2012.

190. Dean JP, Yu EY, Beauchene S, Hall S, Higano CS. Initial Experience with sipuleucel-T (sip-T) in the immediate post-approval setting: the University of Washington (UW) experience. *J Clin Oncol* 30, 2012 (suppl; abstr e15206). Presented at ASCO Annual Meeting, Chicago, June 2012.

191. Hahn NM, Sarantopoulos J, Higano CS, Zhou X, Zhang B, Leonard EJ, Benaim E, Graff J. MLN8237 (alisertib), an investigational Aurora A kinase (AAK) inhibitor, in patients with advanced solid tumors including castration-resistant prostate cancer (CRPC) receiving a standard docetaxel regimen: Preliminary phase 1 results. (ESMO abstr 32277F) Presented at ESMO Congress, Vienna, Austria, September 2012.

192. Smith MR, Antonarakis ES, Ryan CJ, Berry W, Shore ND, Liu G, Alumkal J, Higano C, Chow Maneval E, Rathkopf DE. ARN-509 in Men with High Risk Non-Metastatic Castration-Resistant Prostate Cancer. Proceedings of the European Cancer Congress, Abstract #3109. Presented at ESMO Congress, Vienna, Austria, September 2012.

193. Small EJ, Wesley JD, Quinn D, Higano CS, Lin D, Haynes H, Stewart F, Trager J, Sheikh N. Antigen Presenting Cell (APC) Activation in Sipuleucel-T: Is activation increased in earlier prostate cancer disease states? Proceedings of the European Cancer Congress, Abstract #2870. Presented at ESMO Congress, Vienna, Austria, September 2012.

194. Nguyen HM, Corey E, Morrissey C, Nelson PS, Zhang X, Plymate SR, Higano CS, Lange PH, Roudier MP, True LD, Vessella RL. The biological and molecular characterization of 28 unique prostate cancer xenograft lines (LuCaP series), including responses to therapy. *Cancer Research*: February 6, 2012; Vol 72; C34. Abstract #305. Presented at Annual Prostate Cancer Foundation Scientific Retreat, Carlsbad CA, October 2012.

195. Small EJ, Wesley JD, Quinn D, Higano CS, Lin D, Haynes H, Stewart F, Trager J, Sheikh N. Antigen presenting cell (APC) activation in sipuleucel-T: is activation increased in early prostate cancer disease states? Presented at SUO Annual Meeting, Bethesda, MD. November 2012.

196. Higano CS, Kantoff PW, Whitmore JB, Frohlich MW, Petrylak DP, Small EJ. Sipuleucel-T delays time to first use of opioid analgesics in patients with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer. Presented at SUO Annual Meeting, Bethesda, November 2012.

197. Yu EY, Kuo KF, Hunter-Merril R, Gulati R, Cheng HH, Flamiatos JF, Gambol TE, Hall SP, Higano CS. A Pilot Study of High-dost Exisulind in Men with Biochemical Relaps (BCR) of Prostate Cancer after Definitive Local Therapy Treated with Intermittent Androgen Deprivation (IAD). *J Clin Oncol* 31, 2013 (suppl 6; abstr 209). Presented at Annual ASCO Genitourinary Cancers Symposium, Orlando, February 2013.

198. Small EJ, Higano CS, Kantoff PW, Whitmore JB, Frohlich MW, Petrylak DP. Relationship of sipuleucel-T with time to first use of opioid analgesics (TFOA) in patients (pts) with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC) on the IMPACT trial. *J Clin Oncol* 31, 2013 (suppl 6; abstr 74). Presented at ASCO Genitourinary Cancers Symposium, Orlando, February 2013.

199. Barnett CM, Heinrich MC, Nelson DA, Lim JY, Beadling C, Warrick A, Neff T, Thomas G, Barzotto M, Higano CS, Beer TM, Qian DZ. Genomic analysis of prostate cancer. *J Clin Oncol* 31, 2013 (suppl 6; abstr 80). Presented at ASCO Genitourinary Cancers Symposium, Orlando, February 2013.

200. Sartor AO, Cooperberg MR, Vogelzang NJ, Scholz MC, Concepcion RS, Berry WR, Pieczonka C, Dakhil SR, Vacirca JL, Sandler A, McCoy C, Whitmore JB, Tyler RC, Higano CS. Real-world experience with sipuleucel-T in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) who received prior docetaxel (D): Data from PROCEED. *J Clin Oncol* 31, 2013 (suppl 6; abstr 30^). Presented at ASCO Genitourinary Cancers Symposium, Orlando, February 2013.

201. Gardner TA, Petrylak D, Corman J, Hall S, Weinstein R, Rarick M, Keyser R, Sims R, Sanders A, Sheikh N, DeVries T, Higano C. Immune response with sipuleucel-T in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC): phase 2 ProACT study. Presented at EAU Annual Meeting, Milan Italy, March 2013.

202. Chevillet JR, Gallichotte EN, Cheng HH, Arroyo JD, Briggs LH, Noteboom J, Vessella RL, Higano CS, Yu EY, Pogosova-Agadjanyan EL, Stirewalt DL, Vojtech LN, Hladik F, Tewari M. Circulating microRNA biomarkers for cancer exist in multiple biophysical states. *Cancer Research*: April 15, 2013; Volume 73, Issue 8, Supplement 1 doi: 10.1158/1538-

7445.AM2013-1118. Presented at AACR Annual Meeting, Washington DC, April 2013.

203. Zhang X, Coleman I, Coleman R, Doan K, Roudier M, Chery L, Noteboom J, Higano C, True L, Lange P, Nelson P, Vessella R, Morrissey C. Characterizing the molecular profile of the neuroendocrine phenotype in castration resistant prostate cancer. *Cancer Research*: April 15, 2013; Volume 73, Issue 8, Supplement 1 doi: 10.1158/1538-7445.AM2013-406 Abstr 406/poster board #17. Presented at AACR Annual Meeting, Washington DC, April 2013.

204. Roudier M, Coleman I, Zhang X, Coleman R, Chéry L, Higano C, True LD, Lange PH, Srivastava S, Üren A, Corey E, Vessella RL, Nelson PS, Morrissey C. Characterizing the Molecular Features of ERG Positive Tumors in Primary and Castration Resistant Prostate Cancer. *Cancer Research*: April 15, 2013; Volume 73, Issue 8, Supplement 1 doi: 10.1158/1538-7445.AM2013-5122 Abstr 5122/poster board #21. Presented at AACR Annual Meeting, Washington DC, April 2013.

205. Nguyen HM, Corey E, Morrissey C, Nelson PS, Zhang X, Plymate SR, Higano CS, Lange PH, Roudier MP, True LD, Vessella RL. The biological and molecular characterization of 28 unique prostate cancer xenograft lines (LuCaP series), including responses to therapy. Abstr 305/poster board #3. *Cancer Res* February 6, 2012 72; C34. Presented at AACR Annual Meeting, Washington DC, April 2013.

206. Hirata Y, Akakura K, Higano CS, Bruchovsky N, Aihara K. Mathematical modeling of prostate cancer to personalize intermittent androgen suppression. Presented at "Math Way into Cancer" conference, Spain, May 2013.

207. Cooperberg M, Sartor O, Pieczonka C, Concepcion RS, Kassabian V, Tutrone R, Bailen J, Shore N, Karsh L, Hertzman B, Penson D, McCoy C, Sandler A, Tyler R, Whitmore J, Higano CS. Treatment Practice Patterns in Metastatic Castration-Resistant Prostate Cancer (mCRPC) Patients Prior to Receiving Sipuleucel-T: Data from PROCEED. *J Urol* The Vol. 189, Issue 4, Supplement, Pages e399-e400. Presented at AUA Annual Meeting, San Diego, May 2013.

208. Gardner TA, Petrylak D, Corman J, Hall S, Weinstein R, Sims R, DeVries T, Higano C. Safety and changes in laboratory parameters associated with sipuleucel-T in patients with metastatic castration-resistant prostate cancer: phase 2 ProACT study. *J Urol* The Vol. 189, Issue 4, Supplement, Page e399. Presented at AUA Annual Meeting, San Diego, May 2013.

209. Eapen S, Andrews RM, Gorin B, Higano CS. The economic burden of metastatic castration-resistant prostate cancer – U.S. Medicare perspective. *J Clin Oncol* 31, 2013 (suppl; abstr e16025). Presented at ASCO Annual Meeting, Chicago, June 2013.

210. Higano CS, Armstrong AJ, Cooperberg MR, Kantoff PW, Bailen J, Concepcion RS, Kassabian V, Dakhil SR, Finkelstein SE, Vacirca JL, Rifkin RM, Sandler A, McCoy C, Whitmore JB, Tyler RC, Sartor AO. Impact of prior docetaxel (D) on sipuleucel-t (sip-T) product parameters in proceed patients (pts). *J Clin Oncol* 31, 2013 (suppl; abstr 5034). Presented at ASCO Annual Meeting, Chicago, June 2013.

211. Scher HI, Smith MR, Sweeney C, Corn PG, Logothetis C, Vogelzang NJ, Smith DC, Hussain M, George DJ, De Bono JS, Higano CS, Small EJ, Goldin J, Brown MS, Aftab DT, Noursalehi M, Weitzman A, Basch EM. An exploratory analysis of bone scan lesion area (BSLA), circulating tumor cell (CTC) change, pain reduction and overall survival (OS) in patients (pts) with castration-resistant prostate cancer (CRPC) treated with cabozantinib (cabo): Updated results of a phase 2 non-randomized expansion (NRE) cohort. *J Clin Oncol* 31, 2013 (suppl; abstr 5026). Presented at ASCO Annual Meeting, Chicago, June 2013.

212. Danila DC, Szmulewitz RZ, Higano CS, Gilbert H, Kahn RS, Wood K, Agarwal P, Lin K, Kabbarah O, Fine BM, Maslyar DJ, Vaishampayan UN. A phase I study of the safety and pharmacokinetics of DSTP3086S, an anti-STEAP1 antibody-drug conjugate (ADC), in patients (pts) with metastatic castration-resistant prostate cancer (CRPC). *J Clin Oncol* 31, 2013 (suppl; abstr 5020). Presented at ASCO Annual Meeting, Chicago, June 2013.

213. Yu EY, Duan F, Muzi M, Gorelick J, Chin BB, Alumkal JJ, Taplin ME, Herman B, Higano CS, Doot RK, Harfeil, Febbo PG, Mankoff DA. Correlation of ^{18}F-fluoride PET response to dasatinib in castration-resistant prostate cancer bone metastases correlates with progression-free survival: Preliminary results from ACRIN 6687. *J Clin Oncol* 31, 2013 (suppl; abstr 5003). Oral presentation at ASCO Annual Meeting, Chicago, June 2013.

214. Ahaghotu C, Horton S, Higano CS, Sartor O, Cooperberg MR, Concepcion RS, Dhawan M, Goel S, Hall SJ, Armstrong AJ, Penson DF, Sandler A, McCoy C, Whitmore JB, Tyler RC, Sheikh N, Nabhan C. Disparaties in disease characteristics between Caucasions (CAU) and African Americans (AA) with metastatic castration-resistant prostate cancer (mCRPC)

receiving sipuleucel-T: Data from PROCEED. Presented at the Mid-Atlantic and Western AUA sectional meetings, 2013.

215. Roudier M, Coleman I, Zhang X, Lam H-M, Coleman R, Chéry L, Higano C, True LD, Lange PH, Corey E, Srivastava S, Üren A, Snyder L, Vessella RL, Nelson PS, Morrissey C. Identifying common molecular features of ERG positive tumors in primary and castration resistant prostate cancer. Abstract and poster presented at the Prostate Cancer Foundation Retreat, October 2013.

216. Nabhan C, Sartor O, Cooperberg MR, Armstrong AJ, Vacirca JL, Concepcion RS, Berry WR, Dhawan M, Tutrone R, Sandler A, McCoy C, Whitmore JB, Tyler RC, Higano CS. Real-world experience with Sipuleucel-t in metastatic castration-resistant prostate cancer (mCRPC) patients ≥80 years-old: Data from PROCEED. *J Clin Oncol* 31, 2013 (suppl 6; abstr 131^) Poster displayed at the annual Mid Atlantic AUA Annual Meeting, 2013.

217. Higano CS, Sartor O, Cooperberg MR, Vacirca JL, Concepcion RS, Berry WR, Dhawan M, Tutrone RF, Sandler A, McCoy C, Whitmore JB, Tyler RC, Nabhan C. Real-world experience with Sipuleucel-T in metastatic castration-resistant prostate cancer (mCRPC) patients (pts) ≥80 years-old: data from PROCEED. *J Clin Oncol* 31, 2013 (suppl 6; abstr 131^) Poster presented at Western AUA Annual Meeting, Monterey, November 2013.

218. Finkelstein SE, Nordquist LT, Dakhil SR, Armstrong AJ, Higano CS, Cooperberg MR, Shulman JM, Sims RB, Wang Y, Sartor O. Impact of prior radiation treatment on sipuleucel-T product parameters in Phase 4 PROCEED patients. *J Clin Oncol* 32, 2014 (suppl 4; abstr 183). Presented at ASTRO Annual Meeting, Atlanta, September 2013.

219. Small EJ, Wesley JD, Quinn D, Higano CS, Lin D, Haynes H, Stewart F, Trager J, Sheikh N. Antigen Presenting Cell (APC) Activation in Sipuleucel-T: Is activation increased in earlier prostate cancer disease states? Presented at ESMO, Amsterdam, September 2013.

220. Roudier M, Morrissey C, Dowell A, Corey E, True LD, Higano CS, Vessella RL. Presence of Giant Osteoclasts in Zoledronic Acid Treated Prostate Cancer Bone Metastasis. Poster #SA0460. Presented at ASBMR Annual Meeting, Baltimore, October 2013.

221. Cooperberg MR, Sartor O, Pieczonka CM, Concepcion RS, Kassabian V, Tutrone RF, Bailen JL, Shore ND, Karsh LI, Hertzman BL, Penson DF, McCoy C, Sandler A, Tyler RC, Whitmore JB, Higano CS. Treatment practice patterns in metastatic castration-resistant prostate cancer (mCRPC) patients prior to receiving Sipuleucel-T: Date from PROCEED. *J Urol* The Vol. 189, Issue 4, Supplement, Pages e399-e400. Presented at SUO Annual Meeting, Bethesda, December 2013.

222. Higano CS, Armstrong AJ, Cooperberg MR, Kantoff PW, Bailen JL, Concepcion RS, Kassabian V, Dakhil SR, Finkelstein SE, Vacirca JL, Rifkin RM, Sandler A, McCoy C, Whitmore JB, Tyler RC, Sartor O. Impact of prior Docetaxel (D) on sipuleucel-T (SIP-T) product parameters in PROCEED patients (PTS). *J Clin Oncol* 31, 2013. Poster 65 presented at SUO Annual Meeting, Bethesda, December 2013.

223. Crawford D, Shore N, Higano C, Nejiber A, Yankov V. Intermittent androgen deprivation with the gonadotrophin–releasing hormone antagonist degarelix. Presented at SUO Annual Meeting, Bethesda, December 2013.

224. Drake C, Fan L-Q, GuhaThaKurta D, Stewart F, Kantoff P, Small E, Gardner T, Sheikh N, Trager J, Higano C. Antigen spread and overall survival in advanced prostate cancer patients after treatment with sipuleucel-T. *J Clin Oncol* 32, 2014 (suppl 4; abstr 88). Presented at ASCO-GU Annual Meeting, San Francisco, January 2014.

225. Beer TM, Armstrong AJ, Sternberg CN, Higano CS, Iversen P, Loriot Y, Rathkopf DE, Bhattacharya S, Carles J, De Bono JS, Evans CP, Joshua AM, Kim C-S, Kimura G, Mainwaring PN, Mansbach HH, Miller K, Noonberg SB, Venner PM, Tombal B. Enzalutamide in patients with chemotherapy-naïve metastatic prostate cancer: Results from the phase 3 prevail study. *J Clin Oncol* 32, 2014 (suppl 4; abstr LBA1^). Presented at ASCO-GU Annual Meeting, San Francisco, January 2014.

226. Sarantopoulos J, Hahn NM, Higano CS, Leonard J, Zhang B, Zhou X, Ullman CD, Graff JN. Phase 1 trial of the investigational aurora a kinase (AAK) inhibitor MLN8237 (alisertib) in combination with docetaxel (DTX) in patients (pts) with advanced solid tumors, including castration-resistant prostate cancer (CRPC). *J Clin Oncol* 32, 2014 (suppl 4; abstr 217). Presented at ASCO-GU Annual Meeting, San Francisco, January 2014.

227. Nabhan C, Sartor O, Cooperberg MR, Armstrong AJ, Vacirca JL, Concepcion RS, Berry WR, Dhawan M, Tutrone R, Sandler A, McCoy C, Whitmore JB, Tyler RC, Higano CS. Sipuleucel-t in metastatic castration-resistant prostate cancer (mCRPC) patients ≥80 years-old: Data from PROCEED. *J Clin Oncol* 32, 2014 (suppl 4; abstr 64). Presented at ASCO-

GU Annual Meeting, San Francisco, January 2014.

228. Finkelstein SE, Nordquist LT, Shaker RD, Green NB, Heath EI, Tutrone RF, Vogelzang NJ, Armstrong AJ, Cooperberg MR, Tyler RC, Sims RB, Whitmore JB, Higano CS. Impact of prior radiation treatment (tx) on sipuleucel-T (sip-T) product parameters in PROCEED patients (pts). *J Clin Oncol* 32, 2014 (suppl 4; abstr 183) Presented at ASCO-GU Annual Meeting, San Francisco, January 2014.

229. Vogelzang NJ, Vacirca JL, Kantoff PW, Scholz MC, Dakhil SR, Nordquist LT, Higano CS, Sartor O, Cooperberg MR, Sandler A, McCoy C, Whitmore JB, Tyler RC, Armstrong AJ. Effect of prior abiraterone (ABI) or enzalutamide (ENZ) on sipuleucel-t (sip-T) manufacture in PROCEED patients (pts). *J Clin Oncol* 32, 2014 (suppl 4; abstr 185). Presented at ASCO-GU Annual Meeting, San Francisco, January 2014.

230. Crawford D, Shore N, Higano CS, Nejiber A, Yankov V. Intermittent androgen deprivation with the gonadotrophin–releasing hormone antagonist degarelix. Presented at the 24th International Prostate Cancer Update, Vail, February 2014. Abstract: PD27-05. Presented at AUA Annual Meeting, Orlando, May 2014.

231. Yu EY, Tangen CM, Higano CS, Li H, Yan J, Vogelzang NJ, Hussain M, Thompson IM, Tewari M, Cheng HH. Plasma microRNAs and circulating tumor cells as prognostic biomarkers for patients with new metastatic hormone-sensitive prostate cancer, prospective data from SWOG 0925. Presented at 7th Annual IntraSPORE Prostate Cancer Program Retreat, Fort Lauderdale, March 2014.

232. Vogelzang N, Dakhil S, Armstrong A, Concepcion R, Vacirca J, Pieczonka C, Tutrone R, Nordquist L, Berry W, Penson D, Bailen J, Olsson C, Kantoff P, Cooperberg M, Sartor O, McCoy C, Sandler A, Tyler R, Whitmore J, Higano CS. Real-world experience with patients (pts) receiving Sipuleucel-T: PROCEED data trends over time. Presented at EAU Annual Meeting, 2014.

233. Hall S, Avakian E, Kantoff P, Gardner T, Drake C, Higano C. Sipuleucel-T-induced antigen spread: immune response to prostate-specific antigen correlates with improved overall survival. Abstract: PD27-04. Presented at AUA Annual Meeting, Orlando, May 2014.

234. Yu EY, Tangen CM, Higano CS, Agarwal N, Pal SK, Alva A, Heath EI, Lam ET, Gupta S, Lilly MB, Inoue Y, Chi KN, Vogelzang NJ, Quinn DI, Li H, Cheng HH, Plymate SR, Maha Hussain, Thompson, Jr IM. SWOG S0925: A randomized phase 2 study of androgen deprivation combined with cixutumumab (IMC-A12) versus androgen deprivation alone for patients with new metastatic hormone-sensitive prostate cancer. *J Clin Oncol* 32:5s, 2014 (suppl; abstr 5006). Presented at ASCO Annual Meeting, Chicago, June 2014.

235. Agarwal N, Tangen CM, Hussain M, Lara Jr P, Higano CS, Vaena DA, MacVicar GR, Li H, Crispino T, Quinn DI, Vogelzang NJ, Thompson Jr IM. SWOG S1216: A phase III randomized trial comparing androgen deprivation therapy (ADT) + TAK-700 with ADT + bicalutamide in patients with newly diagnosed metastatic hormone sensitive prostate cancer (HSPC). *J Clin Oncol* 32:5s, 2014 (suppl; abstr TPS5102). Presented at ASCO Annual Meeting, Chicago, June 2014.

236. Danila DC, Szmulewitz RZ, Baron A, Higano CS, Gilbert H, Bernstein F, Lemahieu V, Kabbarah O, Fine BM, Maslyar DJ, Vaishampayan U. A Phase I Study of DSTP3086S, an Antibody-Drug Conjugate (ADC) Targeting STEAP-1 in patients (pts) with Metastatic, Castration-Resistant Prostate Cancer (CRPC). *J Clin Oncol* 32:5s, 2014 (suppl; abstr 5024). Presented at ASCO Annual Meeting, Chicago, June 2014.

237. Armstrong A, Tombal B, Sternberg CN, Higano C, Rathkopf DE, Loriot Y, Saad F, Joshua AM, De Bono J, Venner P, Carles J, Mainwaring P, Evans CP, Noonberg SB, Mansbach H, Bhattacharya S, Perabo F, Phung D, Beer TM. Primary, secondary and quality-of-life endpoint results from PREVAIL, a phase 3 study of enzalutamide in men with metastatic castration resistant prostate cancer. *J Clin Oncol* 32:5s, 2014 (suppl; abstr 5007). Presented at ASCO Annual Meeting, Chicago, June 2014.

238. Morris MJ, Loriot Y, Beer TM, Higano C, Armstrong A, Sternberg CN, De Bono J, Tombal B, Noonberg SB, Mansbach H, Bhattacharya S, Perabo F, Phung D, Rathkopf DE. Sensitivity analyses for radiographic progression-free survival (rPFS): results from the phase 3 PREVAIL trial comparing enzalutamide to placebo. *J Clin Oncol* 32:5s, 2014 (suppl; abstr 5054). Presented at ASCO Annual Meeting, Chicago, June 2014.

239. Haider MA, Morrissey C, Coleman I, Zhang X, Brown L, Kollath L, Koochekpour S, Lange PH, Higano CS, Nelson P, Lin DW, Vessella R, Attwood K, Shourideh M, Montgomery RB, True LD, Roudier M. Identifying biomarkers specific to bone metastases in castrate-resistant prostate cancer. *J Clin Oncol* 32:5s, 2014 (suppl; abstr 5092). Presented at

ASCO Annual Meeting, Chicago, June 2014.

240. Cheng HH, Li H, Higano CS, Tangen CM, Agarwal N, Yan J, Vogelzang NJ, Hussain M, Thompson IM, Tewari M, Yu EY. Comparison of plasma microRNAs with CTCs and PSA in patients treated on SWOG S0925, a randomized phase II study of androgen deprivation combined with cixutumumab versus androgen deprivation alone for patients with new metastatic hormone-sensitive prostate cancer. *J Clin Oncol* 32:5s, 2014 (suppl; abstr 5017). Presented at ASCO Annual Meeting, Chicago, June 2014.

241. Finkelstein SE, Nordquist LT, Shaker RD, Green NB, Heath EI, Tutrone RF, Vogelzang NJ, Armstrong AJ, Cooperberg MR, Tyler RC, Whitmore JB, Higano CS. Impact of prior radiation treatment on sipuleucel-T product parameters in PROCEED patients. *J Clin Oncol* 32, 2014 (suppl 4). Presented at ASTRO Annual Meeting, San Francisco, September 2014.

242. Morris MJ, Higano C, Carrasquillo JA, Sweeney C, Antonarakis ES, Shevrin D, Ryan C, Loriot TY, Fizazi K, Pandit-Taskar N, Garcia-Vargas J, Lyseng K, Bloma M, Aksnes A-K, Scher HI. Safety of radium-223 dichloride (Ra) with docetaxel (D) in patients (pts) with bone metastases (mets) from castration-resistant prostate cancer (CRPC): a phase 1/2a clinical trial. *Annals of Oncol* 2014 25(suppl 4). Presented at ESMO 2014, Madrid, Spain, September 2014.

243. Higano CS, Alumkal J, Chowdhury S, Loriot Y, Sternberg CN, De Bono JS, Tombal B, Carles J, Perabo F, Forer D, Noonberg SB, Mansbach H, Beer TM. Response rates and outcomes with enzalutamide for patients with with metastatic castration resistant prostate cancer and visceral disease in the PREVAIL trial. Annals of Oncol (2014) 25 (suppl 4). Abstract #6343. Presented at ESMO 2014, Madrid, Spain, September 2014.

244. Flaig TW, Mehra M, Potluri R, Ng Y, Todd MB, Higano CS. Real World Data Analysis of Incident Metastatic (M1) Prostate Cancer Patients: US Claims Databse Analysis. *Annals of Oncol* (2014) 25 (suppl 4). Presented at ESMO 2014, Madrid, Spain, September 2014.

245. Loriot Y, Miller K, Sternberg C, Fizazi K, De Bono J, Chowdhury S, Higano CS, Noonberg S, Holmstrom S, Mansbach H, Perabo F, Phung D, Ivanescu C, Skaltsa K, Beer T, Tombal B. Impact of enzalutamide on skeletal related events (SREs), pain and quality of life (QoL) in the PREVAIL trial. Ann Oncol., Volume 29, Issue supple_8, 1 October 2018.*Annals of Oncol* (2014) 25 (suppl4). Presented at ESMO 2014, Madrid, Spain, September 2014.

246. Bracarda S, Procopio G, Parker C, Tombal B, Miller K, Saad F, Fang F, Zhang A, Kornacker M, Higano CS, Smith MR. ERA 223-A Phase 3 Trial of Radium-223 Dichloride (RA-223) in combination with Abiraterone Acetate (AA) and Prednisone in the treatment of asymptomatic or mildly symptomatic Chemotheray naïve patients with bone-predominant mCRPC. Presented at ESMO 2014, Madrid, Spain, September 2014. For encore presentation at Italian Oncology National Congress of AIOM (Italian Association of Medical Oncology), Rome, Italy, October 2015.

247. Ryan CJ, Smith MR, Fizazi K, Saad F, Mulders PFA, Sternberg CN, Miller K, Logothetis CJ, Shore ND, Small EJ, Carles J, Flaig TW, Taplin M-E, Higano CS, De Souza P, De Bono JS, Griffin TW, De Porre P, Yu MK, Park YC, Li J, Kheoh T, Naini V, Molina A and Rathkopf DE. Impact of the O'Brien-Fleming Rule for p Value Allocation on Interpretation of Overall Survival Data in the COU-AA-302 Study. Presented at the PCF Annual Retreat, San Diego, October 2014.

248. Higano CS, Vogelzang NJ, Vacirca J, Kantoff PW, Scholz M, Dakhil SR, Nordquist LT, Sartor O, Cooperberg MR, Sandler A, McCoy C, Whitmore JB, Tyler RC and Armstrong AJ. Effect or Prior Abiraterone (ABI) or Enzalutamide (ENZ) on Sipuleucel-T (SIP-T) manufacture in PROCEED Patients (OTS). Poster presented at WSAUA, Maui, October 2014.

249. DallEra M, Evans CP, Higano CS, Keane T, Andriole G, Saad F, Armstrong A, Noonberg S, Bhattacharya S, Perabo F, Beer T, Tombal B. Enzalutamide in men with metastatic castration-resistant prostate cancer (mCRPC) and visceral disease in the PREVAIL Trial. Presented at Western AUA 2014, Maui, October 2014.

250. Higano CS, Crawford DE, Bosnyak Z, Malmberg A, Neijber A, Klotz L. Risk of cardiovascular events with Degarelix versus Luteinizing hormone-releasing hormone (LHRH) agonists after biochemical relapse of prostate cancer: data from a randomized controlled trial. Presented at SUO 2014, Bethesda, December 2014.

251. Graff JN, Baciarello G, Armstrong AJ, Higano CS, Iversen P, Forer D, Mansbach H, Phung D, Tombal B, Beer TM and Sternberg CN. Clinical Outcomes and Safety in Men ≥ 75 and < 75 Years with Metastatic Castration-Resistant Prostate Cancer (mCRPC) Treated with Enzalutamide in the Phase 3 PREVAIL Trial. *J Clin Oncol* 33, 2015 (suppl 7; abstr 200). Presented at ASCO-GU Annual Meeting, Orlando, February 2015.

252. Ryan CJ, Smith MR, Fizazi K, Saad F, Sternberg CN, Logothetis CJ, Small EJ, Carles J, Flaig TW, Taplin M-E, Higano CS, De Souza P, De Bono JS, Griffin TW, De Porre P, Park YC, Li J, Kheoh T, Molina A and Rathkopf DE. Impact of

crossover and baseline prognostic factors in the COU-AA-302 final analysis (FA). *J Clin Oncol* 33, 2015 (suppl 7; abstr 142). Presented at ASCO-GU Annual Meeting, Orlando, February 2015.

253. Higano CS, Crawford D, Shore N, Bosnyak Z, Malmberg A, Neijber A and Klotz L. Risk of cardiovascular events with degarelix vs leuprolide after biochemical relapse of prostate cancer: exploratory analysis of a randomized controlled trial. *J Clin Oncol* 33, 2015 (suppl 7; abstr 151). Presentated at ASCO-GU Annual Meeting, Orlando, February 2015.

254. Tutrone RF, Ahaghotu CA, Armstrong AJ, Higano CS, Cooperberg MR, Belkoff LH, Olsson CA, Goel S, Tyler RC, Gray TE, McCoy C and Sartor AO. Characteristics of African Americans (AAs) treated with sipuleucel-T (sip-T): comparison of clinical trial and real-world experience. *J Clin Oncol 33, 2015* (suppl 7; abstr 272). Presented at ASCO-GU Annual Meeting, Orlando, February 2015.

255. Hamilton RJ, Ding K, Crook JM, O'Callaghan CJ, Higano CS, Dearnaley D, Horwitz E, Goldenberg L, Gospodarowica MK, Klotz L. The association between statin use and outcomes in patients initiating androgen deprivation therapy. *J Clin Oncol* 33, 2015 (suppl 7; abstr 145). Presented at ASCO-GU Annual Meeting, Orlando, February 2015.

256. Morris MJ, Higano CS, Scher HI, Sweeney C, Antonarakis ES, Shevrin DH, Ryan CJ, Loriot Y, Fizazi K, Pandit-Taskar N, Garcia-Vargas JE, Lyseng K, Bloma M, Aksnes A-K, Carrasquillo JA. Effects of Radium-223 Dichloride (Ra-223) With Docetaxel (D) vs D on Prostate-Specific Antigen (PSA) and Bone Alkaline Phosphatase (bALP) in Patients (pts) With Castration-Resistant Prostate Cancer (CRPC) and Bone Metastases (mets): A Phase 1/2a Clinical Trial. *J Clin Oncol 33,* 2015 (suppl 7; abstr 202). Presented at ASCO-GU Annual Meeting, Orlando, February 2015.

257. Higano CS, Bellmont J, Sternberg C, Tombal B, Kobina S, Vuillez J, Conti P. REASSURE: Radium-223 alpha Emitter Agent in Safety Study in mCRPC polulation for long-term evaluation. Presented at ASCO-GU Annual Meeting, Orlando, February 2015.

258. Sternberg CN, Higano CS, Alumkal J, Chowdhury S, Loriot Y, De Bono JS, Tombal B, Carles J, Perabo F, Forer D, Noonberg SB, Mansbach H and Beer TM. Response rates and outcomes with enzalutamide (ENZA) for patients with metastatic castration-resistant prostate cancer (mCRPC) and visceral disease in the PREVAIL trial. *Annals of Oncol* 25, 2014 (suppl 4). Presented at GCPC/PROSCA, Rome, February 2015.

259. Mulders PFA, Smith MR, Fizazi K, Saad F, Sternberg CN, Miller K, Logothetis CJ, Shore ND, Small EJ, Carles J, Flaig TW, Taplin M-E, Higano CS, de Souza P, de Bono JS, Griffin TW, De Porre P, Yu MK, Park YC, Li J, Kheoh T, Naini V, Molina A, Rathkopf DE and Ryan CJ. Abiraterone acetate improves overall survival in chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC): Impact of crossover and baseline prognostic factors in the COU-AA-302 final analysis. Presented at EAU, Madrid, March 2015.

260. Crawford ED, Higano CS, Shore N, Bosnyak Z, Malmberg A, Neijber A and Klotz L. Risk of cardiovascular (CV) events with degarelix versus luteinizing hormone–releasing hormone (LHRH) agonists after biochemical relapse of prostate cancer (PCa): exploratory analysis of a randomized controlled trial. Presented at AUA, New Orleans, May 2015.

261. Rathkopf, DE, Smith MR, Antonarakis ES, Ryan CJ, Berry WR, Shore ND, Liu G, Higano CS, Alumkal JJ, Hauke R, Tutrone R, Saleh M, Maneval EC, Thomas S, Ricci D, Yu MK, de Boer CJ, Trinh A, Kheoh T, Bandekar R, Scher HI. Androgen Receptor (AR) Mutations in Patients (Pts) with Castration-Resistant Prostate Cancer (CRPC) With and Without Prior Abiraterone Acetate (AA) Treatment. Presented at AACR, Philadelphia, April 2015.

262. Higano CS, Sartor O, Vogelzang N, Dakhil S, Concepcion R, Pieczonka C, Vacirca J, Tutrone R, Olsson C, Penson D, Biggs C, Lill J, Gray T, McCoy C, Cooperberg M, and Armstrong A. Real-world adherence to the 3-dose sipuleucel-T (sip-T) regimen in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). Abstract #146336. Presented at ASCO Annual Meeting, Chicago, May 2015.

263. Beer TM, Armstrong A, Sternberg CN, Higano CS, Rathkopf DE, Loriot Y, Saad F, Joshua AM, De Bono JS, Venner P, Carles J, Mainwaring P, Evans CP, Parli T, Mansbach H, Bhattacharya S, Van Os S, Phung D, and Tombal B. Enzalutamide (ENZA) in Men with Chemotherapy-Naïve Metastatic Castration-Resistant Prostate Cancer (mCRPC): Final Analysis of the Phase 3 PREVAIL Study. *J Clin Oncol* 33, 2015 (suppl; abstr 5036). Presented at ASCO Annual Meeting, Chicago, May 2015.

264. Scher H, Morris MJ, Stadler WM, Higano CS, Halabi S, Smith MR, Basch EM, Fizazi K, Ryan CJ, Antonarakis ES, Corn PG, Liu G, De Bono JS, Schwartz LH, Beer TM, Kelly WK, Hussain M, Sartor AO, Kantoff PW, Armstrong AJ. The Prostate Cancer Working Group 3 (PCWG3) consensus for trials in castration-resistant prostate cancer (CRPC). *J Clin Oncol* 33, 2015 (suppl; abstr 5000). Presented at ASCO Annual Meeting, Chicago, May 2015.

265. Higano CS, Bellmont J, Sternberg CN, Tombal BF, Kobina S, Vuillez JP, Conti P. Radium-223 alpha emitter agent in safety study in mCRPC population for long-term evaluation (REASSURE). Abstract #147996. Presented at ASCO Annual Meeting, Chicago, May 2015.

266. Aggarwal R, Alumkal JJ, Szmulewitz RZ, Higano CS, Bryce AH, Yu MK, De Boer C, Choque-Gonzales G, Small EJ. The role of highly selective androgen receptor (AR) targeted therapy in men with biochemically relapsed hormone sensitive prostate cancer. *J Clin Oncol* 33, 2015 (suppl; abstr TPS5084). Presented at ASCO Annual Meeting, Chicago, May 2015.

267. Smith MR, Parker C, Tombal B, Miller K, Saad F, Fang F, Zhang A, Kornacker M, Higano CS. ERA 223—A Phase 3 Trial of Radium-223 Dichloride (Radium-223) in Combination With Abiraterone Acetate (Abiraterone) and Prednisone in The Treatment of Asymptomatic or Mildly Symptomatic Chemotherapy-Naïve Patients With Bone Predominant Metastatic Castration-Resistant Prostate Cancer (mCRPC). *J Clin Oncol* 33, 2015 (suppl; abstr TPS5082). Presented at ASCO Annual Meeting, Chicago, May 2015.

268. Morris MJ, Higano CS, Scher HI, Sweeney C, Antonarakis ES, Shevrin D, Ryan CJ, Loriot Y, Fizazi K, Pandit-Taskar N, Garcia-Vargas J, Lyseng K, Bloma M, Carrasquillo JA. Effects of Radium-223 Dichloride (Ra-223) With Docetaxel (D) vs D on Prostate-Specific Antigen (PSA) and Bone Alkaline Phosphatase (bALP) in Patients (pts) With Castration-Resistant Prostate Cancer (CRPC) and Bone Metastases (mets): A Phase 1/2a Clinical Trial. *J Clin Oncol* 33, 2015 (suppl; abstr 5012). Presented at Annual ASCO Meeting, Chicago, May 2015.

269. Chi KN, Blumenstein, B, Higano CS, Reeves J, Feyerabend S, Gravis G, Ferrero JM, Jacobs C, de Bono J. Phase 3 SYNERGY trial: docetaxel +/- custirsen and overall survival in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) and poor prognosis. *J Clin Oncol* 33, 2015 (suppl; abstr 5009). Presented at ASCO Annual Meeting, Chicago, May 2015.

270. Goldenberg SL, Wassersug RJ, Pollock P, Zarowski C, Dayan M, Van Patten C, Elliot S, Sundar M, Mahovlich S, Jackowich R, Black P, So A, Higano CS. Implementation of the Prostate Cancer Supportive Care Program (PCSC), a comprehensive approach for men with prostate cancer (PC) and their partners. Support Care Center (2015) 23 (Suppl 1): abstract #S318. Oral presentation at MASCC/ISOO conference, Vienna, Austria, June 2015.

271. Higano CS, Pollock P, Wassersug, RJ, Zarowski C, Dayan M, Weller S, Van Patten C, Elliott S, Sundar M, Mahovlich S, Wibowo E, Gleave M, Black P, So A, Goldenberg L. Successful implementation of a disease specific survivorship program for men with prostate cancer (PC) and their partners. J Clin Oncol 34, 2016 (suppl 3S; abstr 31). Poster presentation, 2016 Cancer Survivorship Symposium, San Francisco, CA, January 2016.

272. Higano CS, Zarowski C, Dayan M, Pollock P, Elliott S, Mahovlich S, Sundar M, Goldenberg L. Utilization of sexual health and pelvic floor physiotherapy services in Vancouver's Prostate Cancer Supportive Care (PCSC) Program. J Clin Oncol 34, 2016 (suppl 3S; abstr 163). Poster presentation 2016 Cancer Survivorship Symposium, San Francisco, CA, January 2016.

273. Higano CS, Armstrong AJ, Cooperberg MR, Concepcion RS, Tutrone RF, Olsson CA, Pieczonka CM, Shore ND, Chang NN, Lill JS, Sartor AO. Analysis of the PROCEED registry by baseline prostate-specific antigen (PSA) quartiles: preliminary analysis of real-world sipuleucel-T (sip-T) use. *J Clin Oncol* 34, 2016 (suppl 2S; abstr 193). Poster presentation, ASCO Genitourinary Cancers Symposium, San Francisco, CA, January 2016.

274. Penson DF, Armstrong AJ, Concepcion RS, Wu K, Wang F, Krivoshik AP, Phung D, Higano CS. Sensitivity analyses for progression-free survival (PFS) and radiographic PFS (rPFS) from the phase 2 STRIVE Trial comparing enzalutamide (ENZA) with bicalutamide (BIC) in men with castration-resistant prostate cancer (CRPC). *J Clin Oncol* 34, 2016 (suppl 2S; abstr 169). Poster presentation, ASCO Genitourinary Cancers Symposium, San Francisco, CA, January 2016.

275. Cheng HH, Klemfuss N, Montgomery RB, Higano CS, Schweizer MT, Mostaghel EA, Yu EY, Nelson P, Pritchard CC. Pilot study of clinical targeted next generation sequencing for prostate cancer: Consequences for treatement and genetic counseling. *J Clin Oncol* 34, 2016 (suppl 2S; abstr 251). Poster presentation, ASCO Genitourinary Cancers Symposium, San Francisco, CA, January 2016.

276. Morris MJ, Beer TM, Loriot Y, Higano CS, Armstrong AJ, Sternberg CN, de Bono JS, Tombal BF, Parli T, Bhattacharya S, Krivoshik AP, Phung D, Rathkopf DE. Correlation between radiographic progression-free survival (rPFS) and overall survival (OS): Results from PREVAIL. *J Clin Oncol* 34, 2016 (suppl 2S; abstr 182). Poster presentation, ASCO Genitourinary Cancers Symposium, San Francisco, CA, January 2016.

277. Armstrong AJ, Higano CS, Sartor AO, Vogelzang NJ, Berry WR, Penson DF, Kassabian V, Nordquist LT, Chang NN, Lill JS, Cooperberg MR. Changing characteristics of patients treated with sipuleucel-T (sip-T) over time: Real-world experience from the PROCEED registry. *J Clin Oncol* 34, 2016 (suppl 2S; abstr 320). Poster presentation, ASCO Genitourinary Cancers Symposium, San Francisco, CA, January 2016.

278. Sartor AO, Cooperberg MR, Armstrong AJ, Vogelzang NJ, Vacirca JL, Scholz MC, Dakhil SR, Nordquist LR, Heath EI, Chang NN, Lill JS, Higano CS. Real-world experience of therapeutic sequencing and time to first anticancer intervention (ACI) following sipuleucel-T (sip-T): Initial data from the PROCEED registry. *J Clin Oncol* 34; 2016 (suppl 2S; abstr 194). Poster presentation, ASCO Genitourinary Cancers Symposium, San Francisco, CA, January 2016.

279. Higano CS, Pollock P, Wassersug RJ, Zarowski C, Dayan M, Weller S, Van Patten C, Elliott S, Sunday M, Mahovlich S, Wibowo E, Gleave M, Black PC, So A, Goldenberg L. Successful implementation of a disease-specific survivorship program for men with prostate cancer (PC) and their partners. *J Clin Oncol* 34, 2016 (suppl 3S; abstr 31). Presented at ASCO 2016 Cancer Survivorship Symposium, San Francisco, CA, January 2016.

280. Higano CS, Zarowski C, Dayan M, Pollock P, Elliott S, Mahovlich S, Sundar M, Goldenberg L. Utilization of sexual health and pelvic floor physiotherapy services in Vancouver's Prostate Cancer Supportice Care (PCSC) Program. *J Clin Oncol* 34, 2016 (suppl 3S; abstr 163). Presented at ASCO Cancer Survivorship Symposium, San Francisco, CA, January 2016.

281. Tombal B, Bellmunt J, Sternberg C, Kobina S, Vuillez JP, Conti, PS, Finkelstein SE, Higano CS. Radium-223 alpha emitter agent in nonintervention safety study in mCRPC population for long-term evaluation (REASSURE). Abstract #41.355. Oral presentation 31st Annual EAU Congress, Munich, Germany, March 2016.

282. Wassersug R, Mahovlich S, Bell R, Sundar M, Higano CS, So A, Pollock P, Goldenberg L. Evaluating whether an educational intervention reduces distress in men with newly-diagnosed prostate cancer and their partners. Oral presentation 10th Annual Lorne D. Sullivan Lectureship & Research Day. Vancouver, BC, June 2016.

283. Higano CS, Pollock P, Wassersug RJ, Zarowski C, Dayan M, Weller S, Van Patten C, Elliott S, Sundar M, Mahovlich S, Wibowo E, Gleave M, Black P, So A, Goldenberg. Implementation of a disease specific survivorship program for men with prostate cancer and their partners. *J Clin Oncol* 34, 2016 (suppl; abstr e21569). Published 2016 ASCO Annual Meeting. Chicago, IL, June 2016.

284. Goldkorn A, Plets M, Agarwal N, Hussain M, Lara P, Vaena DA, MacVicar GR, Crispino T, Harzstark AL, Twardowski P, Tangen CM, Hugen CM, Xu T, Xu Y, Pinski JK, Ingles SA, Higano CS, Vogelzang NJ, Thompson IM, Quinn DI. Circulating tumor cells (CTCs) in SWOG S1216: A phase 3 multi-center trial in metastatic hormone sensitive prostate cancer (mHSPC). *J Clin Oncol* 34, 2016 (suppl; abstr 11516). Poster presentation 2016 ASCO Annual Meeting. Chicago, IL, June 2016.

285. Pond GR, Sonpavde G, Plets M, Tange CM, Hussain M, Lara P, Goldkorn A, Garsotto M, Mack PC, Higano CS, Vogelzang NJ, Thompson IM, Twardowski P, Van Veldhuizen PR, Agarwal N, Carducci MA, Monk P, Quinn DI. Validation of the association of RECIST 1.0 changes with survival in men with metastatic castration resistant prostate cancer (mCRPC) treated on SWOG study S0421. *J Clin Oncol* 34, 2016 (suppl; abstr 5079). Poster presentation 2016 ASCO Annual Meeting. Chicago, IL, June 2016.

286. Armstrong AJ, Higano CS, Cooperberg MR, Ahaghotu CA, Tutrone RF, Belkoff LH, Olsson CA, Goel S, Tyler RC, Chang NN, Lill JS, Sartor O. Characteristics and anticancer therapies (ACIs) of African American (AA) and Caucasian (CAU) patients (pts) treated with sipuleucel-T: real-world experience from the PROCEED registry. *J Clin Oncol* 34, 2016 (suppl; abstr 5025). Poster presentation 2016 ASCO Annual Meeting. Chicago, IL, June 2016.

287. Morris MF, Fizazi K, Sweeney C, Loriot Y, Ryan CJ, Shevrin D, Antonarakis ES, Reeves J, Chandrawansa K, Kornacker M, Higano CS. Updated results: a phase I/IIa randomized trial of radium-223 + docetaxel versus docetaxel in patients with castration-resistant prostate cancer and bone metastases. *J Clin Oncol* 34, 2016 (suppl; abstr 5075). Poster presentation 2016 ASCO Annual Meeting. Chicago, IL, June 2016.

288. Smith MR, Parker C, Tombal B, Miller K, Saad F, Shen JW, Zhang A, Kornacker M, Higano CS. ERA 223: A phase 3 trial of radium-223 dichloride in combination with abiraterone acetate and prednisone in the treatment of asymptomatic or mildly symptomatic chemotherapy-naïve patients with bone-predominant metastatic castration-resistant prostate cancer. *J Clin Oncol* 34, 2016 (suppl; abstr TPS5088). Poster presentation 2016 ASCO Annual Meeting. Chicago, IL, June 2016.

289. Vogelzang NJ, Armstrong AJ, Higano CS, Sartor AO, Pieczonka CM, Concepcion RS, Tutrone RF, Olsson CA, Bailen JL, Penson DF, Chang NN, Lill JS, Tyler RC, Cooperbert MR. Treatment patterns for metastatic castration-resistant prostate cancer (mCRPC) in oncology (ONC) urology (URO) practices: Data from the PROCEED registry. *J Clin Oncol* 34, 2016 (suppl; abstr e16503). Published 2016 ASCO Annual Meeting. Chicago, IL, June 2016.

290. Higano, CS, Zarowski C, Dayan M, Pollock P, Elliott S, Mahovlich S, Sundar M, Goldenberg L. Utilization of sexual health and pelvic floor physiotherapy services in Vancouver's Prostate Cancer Supportive Care (PCSC) Program. *J Clin Oncol* 34, 2016 (suppl; abstr 10108). Poster presentation, 2016 ASCO Annual Meeting. Chicago, IL, June 2016.

291. Pieczonka CM, Vogelzang NJ, Nordquist LT, Mehlhaff BA, Kassabian V, Williams M, Armstrong AJ, Cooperberg MR, Chang NN, Lill JS, Higano CS. Treatment Patterns and Therapy Sequences in Community-Based Clinics and Teaching Hospitals: an Analysis from the PROCEED Registry. Submitted for presentation, 2016 AUA Annual Meeting, San Diego, CA, 2016.

292. Elliott S, Zarowski C, Dayan M, Pollock P, Spillane M, Mahovlich S, Sundar M, Higano CS, Goldenberg L. The utilization of a dedicated sexual health and pelvic floor physiotherapy service for urinary incontinence and erectile dysfunction after prostate cancer diagnosis. Abstract #88. Accepted for presentation, 2016 Sexual Medicine Society of North America (SMSNA) meeting. Phoenix, AZ, November 2016.

293. Weller S, Spillane M, Pollock P, Sundar M, Goldenberg L, Hedden L, Higano CS. Implementation of an exercise behavior change clinic for men with prostate cancer: Baseline results. *J Clin Oncol 35*, 2017 (suppl 5S; abstr 169). Poster presentation, ASCO Cancer Survivorship Symposium, San Diego, CA, January 2017.

294. Hedden L, Wassersug RJ, Mahovlich S, Pollock P, Sundar M, Bell RH, Goldenberg L, Higano CS. Evaluating an Educational Intervention to Alleviate Distress among Men with Newly-Diagnosed Prostate Cancer and their Partners. *J Clin Oncol* 35, 2017 (suppl 5S; abstr 194). Poster presentation, ASCO Cancer Survivorship Symposium, San Diego, CA January 2017.

295. Rosenberg D, Kadokura EA, Bouldin ED, Miyawaki CE, Higano CS, Hartzler AL. Acceptability of Fitbit for physical activity tracking within clinical care among men with prostate cancer. AMIA Annu Symp Proc. 2017 Feb 10;2016:1050-1059. eCollection 2016.

296. Armstrong, AJ, Lin P, Higano CS, Sternberg CN, Sonpavde G, Tombal BF, Templeton AJ, Fizazi F, Phung D, Wong EK, Krivoshik A, Beer TM. Development and validation of a prognostic model for overall survival in chemotherapy-naïve ment with metastatic castration-resistant prostate cancer (mCRPC) from the phase III PREVAIL clinical trial. *J Clin Oncol* 35, 2017 (suppl 6S; abstract 138). Poster presentation, ASCO Genitourinary Cancers Symposium, Orlando, FL, February 2017.

297. Armstrong AJ, Higano CS, Sartor O, Penson DF, Vogelzang NJ, Dakhil SR, Pieczonka CM, Vacirca JL, Tutrone RF, Nordquist LT, Chang NN, Cooperberg MR. Relationship between smoking, prognostic factors, and outcomes in patient (pts) with metastatic castration-resistant prostate cancer (mCRPC) receiving sipuleucel-T (sip-T): Preliminary analysis of the PROCEED registry. *J Clin Oncol* 35, 2017 (suppl 6S; abstract 216). Poster presentation, ASCO Genitourinary Cancers Symposium, Orlando, FL, February 2017.

298. Morris MJ, Loriot Y, Fizazi K, Sweeney C, Ryan CJ, Shevrin DH, Antonarakis ES, Seger M, Lu C, Higano CS. Effects of radium-223 (Ra-223) with docetaxel versus docetaxel alone on bone biomarkers in patients with bone-metastatic castration-resistant prostate cancer (CRPC): A phase I/IIa clinical trial. *J Clin Oncol* 35, 2017 (suppl 6S; abstract 154). Poster presentation, ASCO Genitourinary Cancers Symposium, Orlando, FL, February 2017.

299. Armstrong AJ, Lin P, Higano CS, Iversen P, Sternberg CN, Tombal B, Phung D, Parli T, Krivoshik A, Beer TM. Prognostic Associates of Prostate-Specific Antigen (PSA) Decline With Survival, Radiographic Response andProgression in Chemotherapy-Naïve Men With Metastatic Castration-Resistant Prostate Cancer (mCRPC) Treated With Enzalutamide. Abstract #2105. Submitted for presentation, ESMO Congress 2017, Madrid, Spain, September 2017.

300. Zarowski C, Hedden L, Spillane M, Pollock P, Goldenberg L, Higano CS, Elliott A. A Study Protocol for a Critical Appraisal of The Sexual Health Rehabilitation Action Plan (SHRAP). Abstract #324. Moderated poster presentation, 2017 Annual Fall Scientific Meeting of the SMSNA, San Antonio, TX, October 2017.

301. Beer TM, Chowdhury S, Saad F, Shore, ND, Higano CS, Iversen P, Fizazi K, Miller K, Heidenreich A, Kim CS, Phung D, Barrus J, Nikolayeva N, Krivoshik A, Waksman J, Tombal B. Hepatic effects assessed by review of safety data in

enzalutamide castration-resistant prostate cancer (CRPC) trials. *J Clin Oncol* 36, 2018 (suppl 6S; abstr 199). Poster presentation, ASCO 2018 Genitourinary Cancers Symposium, San Francisco, CA, February 2018.

302. Harshman LC, Sartor AO, Richardson T, Sylvester J, Song DY, Mantz C, Brookland RK, Perlmutter M, Given R, Kalinovsky J, Babajanyan S, De Sanctis Y, Higano CS. First Interim Results of the Radium-223 (Ra-223) REASSURE Observational Study in Metastatic Castration-Resistant Prostate Cancer (mCRPC): Safety and Baseline (BL) Characteristics of US Patients (Pts) by Prior/Concomitant Treatment (Tx). *J Clin Oncol* 36, 2018 (suppl 6S; abstr 233). Poster presentation, ASCO 2018 Genitourinary Cancers Symposium, San Francisco, CA. February 2018.

303. Hedden L, Pollock P, Sundar M, So A, Black PC, Gleave M, Goldenberg L, Higano CS. Patterns & Predictors of Attendance at a Comprehensive, Multi-Disciplinary Supportive Care Program for Men with Prostate Cancer & Their Partners. *J Clin Oncol* 36, 2018 (suppl 7S; abstr 6). Poster presentation, ASCO 2018 Cancer Survivorship Symposium, Orlando, FL. February 2018.

304. Bossio J, Zarowski C, Elliott S, Hedden L, Pollock P, Spillane M, Wu E, Nunez N, Branch A, Goldenberg L, Higano CS. Utilization of the Sexual Health Service from the Prostate Cancer Supportive Care Program: A chart review. *J Clin Oncol* 36, 2018 (suppl 7S; abstr 137). Poster presentation, ASCO 2018 Cancer Survivorship Symposium, Orlando, FL. February 2018.

305. Spillane M, Pollock P, Hedden L, Wu E, Goldenberg L, Jones JM, Matthew A, Truong T, Gavrylyuk Y, Higano CS. Implementation of an electronic patient reported outcome system in a prostate cancer urology clinic. *J Clin Oncol* 36, 2018 (suppl 7S; abstr 143). Poster presentation, ASCO 2018 Cancer Survivorship Symposium, Orlando, FL. February 2018.

306. McLaughlin K, Hedden L, Pollock P, Higano CS, Murphy RA. Nutrition services for Men with Prostate Cancer: a health professional survey. *J Clin Oncol* 36, 2018 (suppl 7S; abstr 25). Poster presentation, ASCO 2018 Cancer Survivorship Symposium, Orlando, FL. February 2018.

307. Ramirez A, Ericson N, Campton D, Duplessis M, Mojica TM, Clein A, Higano CS, Gadi VK, Sabath DE, Kaldjian E. Development of a multi-parameter immunofluorescence assay for identification of circulating tumor cells with epithelial-mesenchymal phenotype. Abstract submitted for presentation, AACR 2018 Annual Meeting, Chicago, IL, April 2018.

308. Sun Y, Campton D, Ramirez A, Mojica TM, Clein A, Higano CS, Sabath DE, Kaldjian E. Increased phenotypic depth for automated visual identification of biomarkers on circulating tumor cells by cocktailing epithelial markers EpCAM and cytokeratin. Abstract submitted for presentation, AACR 2018 Annual Meeting, Chicago, IL, April 2018.

309. Sartor AO, Higano CS, Cooperberg MR, Vogelzang NJ, Dakhil SR, Pieczonka CM, Vacirca J, Concepcion RS, Trutrone RF, Nordquist LT, Olsson CA, Penson DF, Schnadig I, Bailen JL, Behlhaff B, Chang NN, Sheikh NA, Brown B, Armstrong AJ. *J Clin Oncol* 36, 2018 (suppl; abstr 5041). Poster presentation, ASCO 2018 Annual Meeting, Chicago, IL. June 2018.

310. Halabi S, Dutta S, Tangen CM, Rosenthal M, Petrylak DP, Thompson IM, Chi KN, de Bono JS, Fandi A, Araujo JC, Eisenbergher MA, Logothetis C, Quinn DO, Fizazi K, Higano CS, George DJ, Morris MJ, Small EJ, Tannock I, Kelly WK. Overall survival between African-American (AA) and Caucasion © men with metastatic castration-resistant prostate cancer (mCRPC). *J Clin Oncol* 36, 2018 (suppl; abstr LBA5005). Oral presentation, ASCO 2018 Annual Meeting, Chicago, IL. June 2018.

311. Raymond VM, Mojica TM, Harris EV, Lanman RB, Higano CS. Cell-free circulating tumor DNA (cfDNA) to identify germline (GL) and somatic BRCA alterations (alts) in men with advanced prostate cancer (ProsCa). *J Clin Oncol* 36, 2018 (suppl; abstr e24287). Publication only, ASCO 2018 Annual Meeting, Chicago, IL. June 2018.

312. Weller S, Pollock P, Hedden L, Wu E, Spillane M, Sundar M, Goldenberg L, Campbell KL, Higano CS. Impact of prostate cancer treatments on exercise behaviors of men attending an exercise counselling service implemented as standard care. *J Clin Oncol* 36, 2018 (suppl; abstr e22057). Publication only, ASCO 2018 Annual Meeting, Chicago, IL. June 2018.

313. Higano CS, Armstrong AJ, Sartor AO, Vogelzang NJ, Kantoff PW, McLeod DG, Pieczonka CM, Penson DF, Shore ND, Vacirca JL, Concepcion RS, Tutrone RF, Nordquist LT, Quinn DI, Kassabian V, Scholz MC, Tyler RC, Chang NN, Brown B, Cooperberg MR. Cerebrovascular event (CVE) outcome and overall survival (OS) in patients (pts) treated with sipuleucel-T (sip-T) for metastatic castration-resistant prostate cancer (mCRPC): results from the PROCEED registry. *J Clin Oncol* 36, 2018 (suppl; abstr e17018). Publication only, ASCO 2018 Annual Meeting, Chicago, IL. June 2018.

314. Higano CS, Tombal B, Miller K, Saad F, Sartor AO, Tangirala K, Jiao X, Kalinovsky J, Sternberg CN. Clinical outcome with radium-223 (Ra-223) in patients (pts) previously treated with abiraterone (Abi) or enzalutamide (Enza): A retrospective study of real-world (RW) data from pts with metastatic castration-resistant prostate cancer (mCRPC). *Ann Oncol* (2018) 29 (suppl 8). Poster presentation. ESMO Congress 2018, Munich Germany. October 2018.

315. Smith M, Parker C, Saad F, Miller K, Tombal B, Sing Ng Q, Boegemann M, Matveev V, Piulats JM, Zucca LE, Heidenreich A, Kakehi Y, Zhang A, Krissel H, shen J, Wagener V, Higano CS. ERA 223: A phase 3 trial of radium-223 (Ra-223) in combination with abiraterone acetate and prednisone/prednisolone for the treatment of asymptomatic or mildly symptomatic chemotherapy-naïve patients (pts) with bone-predominant metastatic castration-resistant prostate cancer (mCRPC). *Ann of Oncol* (2018) 29 (suppl 8, abstr #2672). Poster presentation. ESMO Congress 2018, Munich Germany. October 2018.

316. Sternberg CN, Tombal B, Miller K, Saad F, Sartor O, Sade JP, Logothetis C, Bellmunt J, Dizdarevic S, Harshman LC, Logue J, Baldari S, Richardson T, Bottomley D, Schostak M, Bayh I, Kalinovsky J, Higano C. Use of bone health agents (BHAs) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) treated with radium-223 (Ra-223) after abiraterone (Abi): An interim review of REASSURE. *Ann of Oncol* (2018) 29 (suppl 8). Poster presetation. ESMO Congress 2018, Munich Germany. October 2018.

317. De Bono JS, Higano C, Saad F, Miller K, Casey M, Czibere A, Healy C, Fizazi K. TALAPRO-1: An open-label, response rate phase II study of talazoparib (TALA) in men with DNA damage repair defects (DDR) and metastatic castration-resistant prostate cancer (mCRPC) who previously received taxane-based chemotherapy (CT) and progressed on $\geq$ 1 novel hormonal therapy (NHT). *Ann of Oncol* (2018) 29 (suppl 8). Poster presentation. ESMO Congress 2018, Munich Germany. October 2018.

318. De Bono JS, Hansen A, Choudhury AD, Cook N, Heath EI, Higano C, Linch M, Martin-Liberal J, Rathkopf DE, Wisinski KB, Barry S, de Bruin E, Brugger W, Colebrook S, Klinowska T, Moschetta M, Mortiner PGS, Siu LL, Shapiro G. AZD8186, a potent and selective inhibitor of PI3Kβ/δ, as monotherapy and in combination with abiraterone acetate plus prednisone (AAP), in patients (pts) with metastatic castrate-resistant prostate cancer (mCRPC). *Ann of Oncol* (2018) 29 (suppl 8). Poster presentation. ESMO congress 2018, Munich Germany. October 2018.

HIGANO SUPPORT

GRANTS - *Current*

PCF Challenge Award (Febbo/Higano) 09/01/2011 – 07/31/2019
Prostate Cancer Foundation
[redacted]
Howard R Soule, PhD | 1250 Fourth St | Santa Monica, CA 90401
A Pilot Study of the Effects of Cabozantinib (XL184) on Bone Turnover and the Microenvironment in Men with Non-Metastatic and Metastatic Castration-Resistant Prostate Cancer
The primary goal is to assess the impact of cabozantinib on markers of bone turnover and microenvironment in men with no evidence of bone metastases.
Role: Co-PI

W81XH-16-PCRP-CCRSA (Higano) 09/30/2017 – 09/29/2020
DOD Prostate Cancer Research Program
[redacted]
USA Med Research Acq Activity I Dana Herndon I 820 Chandler St
Fort Detrick, MD 21702-5014
Prostate Cancer Clinical Trials Consortium – Member Site
The Department of Defense provides funding for infrastructure to participate as a clinical site in the Prostate Cancer Clinical Trials Consortium.
Role: Clinical Site PI

D2017-1893 Movember Discovery Grant (Brotto) 01/01/2017 – 06/30/2019
Prostate Cancer Canada
[redacted]
Stuart Edmonds | 2 Lombard St 3rd Flr | Toronto, ON M5C 1M1
Innovations in the treatment of sexual dysfunction and couple intimacy after prostate cancer: A randomized trial of mindfulness versus cognitive behavioural therapy.

Role: Co-PI

GRANTS - *Pending*

CCSG Early Phase Clinical Research Support Grant (Higano)
Seattle Translational Tumor Research (NCI P30 CA015704-41)
Heidi Tham | 1100 Fairview Ave N | Seattle, WA 98109
Mechanisms of Metabolic and Hormone Action on Plaque Formation in Brain and Carotid Vessels in Men Undergoing Androgen Deprivation Therapy
The primary goal is to measure the impact of androgen deprivation on metabolic, brain and cardiovascular endpoints.
Role: PI

CLINICAL TRIAL CONTRACTS - *Current*

Protocol # MDV3100-03 (Higano) 02/15/2011 – 09/30/2018
Medivation, Inc.
[redacted]
Alicia Tyson | 201 Spear St, 3rd fl | San Francisco, CA 94105
PREVAIL: A Multinational Phase 3, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Oral MDV3100 in Chemotherapy-Naïve Patients with Progressive Metastatic Prostate Cancer who have Failed Androgen Deprivation Therapy.
The primary goals are to determine the benefit of MDV3100 as compared to placebo as assessed by overall survival, and to determine the benefit of MDV3100 as compared to placebo as assessed by radiographic progression-free survival (rPFS).
Role: Site PI

Protocol # MDV3100-09 (Higano) 11/06/2012 - 10/31/2018
Medivation, Inc
[redacted]
Lynn Bui, MD | 525 Market St, 36th fl | San Francisco, CA 94105
STRIVE: A Mulitcenter Phase 2, Randomized, Double-Blind, Efficacy and Safety Study of Enzalutamide vs. Bicalutamide in Men with Prostate Cancer Who Have Failed Primary Androgen Deprivation Therapy
The primary goal is to determine the benefit of enzalutamide (formerly MDV3100) as compared to bicalutamide as assessed by progression-free survival (PFS).
Role: Site PI

Protocol # ARN-509-002 (Higano) 02/15/2013 - 12/31/2018
Aragon Pharmaceuticals, Inc
[redacted]
Rich Heyman | 12780 El Camino Real #301 | San Diego, CA 92130
The Role of Highly Selective Androgen Receptor (AR) Targeted Therapy in Men with Biochemically Relapsed Hormone Sensitive Prostate Cancer
The primary goals are to compare the mean change in QOL as measured by total FACT-P score after 12 months of therapy with ARN-509 monotherapy compared with LHRHa monotherapy in men with BCR, and; to compare the mean change in QOL as measured by total FACT-P score after 12 months of therapy of ARN-509 + LHRHa vs. LHRHa monotherapy in men with BCR.
Role: Site PI

Protocol # D4620C00001 (Higano) 10/01/2013 - 04/30/2019
AstraZeneca AB
[redacted]
1800 Concord Pike | Wilmington, DE 19850
A Phase I, Open-label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-tumor Activity of Ascending Doses of AZD8186 in Patients with Advanced Castrate-resistant Prostate Cancer (CRPC), Squamous Non-Small Cell Lung Cancer (sqNSCLC), Triple Negative Breast Cancer (TNBC) and Patients with Known PTEN-deficient Advanced Solid Malignancies, with Expansion to Assess the Pharmacodynamic Activity of AZD8186 within Prospectively-validated PTEN-deficient Tumors

The primary goal is to investigate the safety and tolerability of AZD8186 when given orally to patients with advanced castrate-resistant prostate cancer (CRPC), squamous non-small cell lung cancer (NSCLC) and triple negative breast cancer (TNBC) and known PTEN-deficient advanced solid malignancies.
Role: Site PI

Protocol # ARN-509-003 (Higano) 01/12/2014 - 12/31/2018
Aragon Pharmaceuticals, Inc
Rich Heyman | 12780 El Camino Real #301 | San Diego, CA 92130
A Multicenter Randomized, Double-Blind, Placebo-Controlled, Phase III Study of ARN-509 in Men with Non-Metastatic (M0) Castration-Resistant Prostate Cancer
The primary goal is to demonstrate superiority in the metastasis-free survival (MFS) of men with high risk NM-CRPC treated with ARN-509 versus placebo.
Role: Site PI

Protocol # 15396 (Higano) 09/17/2014 - 09/16/2019
Bayer Health Care
Montville, NJ
A phase III randomized, double-blind, placebo-controlled trial of Radium-223 dichloride in combination with abiraterone acetate and prednisone/ prednisone in the treatment of asymptomatic or mildly symptomatic chemotherapy-naïve subjects with bone predominant metastatic castration-resistant prostate cancer (CRPC)
The primary goal is to compare, in subjects with asymptomatic or mildly symptomatic chemotherapy-naïve bone predominant metastatic castration-resistant prostate cancer, the clinical benefit of radium-223 dichloride versus placebo in combination with abiraterone and prednisone/prednisolone.
Role: Global PI/Site PI

Protocol # 16544 (Higano) 12/03/2014 - 03/01/2019
Bayer Health Care
Montville, NJ
A Randomized Open-Label Phase IIa Study Evaluating the Efficacy and Safety of Radium-223 Dichloride in Combination with Abiraterone Acetate or Enzalutamide in Subjects with Castration Resistant Prostate Cancer (CRPC) who have Bone Metastases
The primary goal is to describe radiological progression free survival (rPFS) in subjects treated with radium-223 dichloride 50 kBq/kg administered every 4 weeks; radium-223 dichloride 50 kBq/kg administered every 4 weeks together with abiraterone acetate 1000 mg orally daily plus prednisone orally twice daily (bid); or radium-223 dichloride 50 kBq/kg administered every 4 weeks together with enzalutamide 160 mg orally daily.
Role: Site PI

Protocol # 401 (Higano) 12/18/2014 - 12/31/2019
Emergent BioSolutions
Seattle, WA
A Phase 1 Study of ES414 in Patients with Metastatic Castration-Resistant Prostate Cancer
The primary goal is to identify the maximum tolerated dose and determine clinical activity of ES414 in patients with mCRPC that have not received prior chemotherapy.
Role: Site PI

Protocol # 16913 (Higano) 03/16/2016 - 02/29/2024
Bayer Health Care
Kelly Peters I Katnar Health, LLC I 11960 Westline Industrial Dr, Ste 180 I St. Louis, MO 63149
REASSURE – Radium-223 alpha Emitter Agent in Safety Study in mCRPC population for long-term evaluation
The primary goal is to assess the incidence of second primary malignancies among patients with metastatic Castration Resistant Prostate Cancer (mCRPC) receiving Radium-223 in routine clinical practice.
Role: Site PI

Protocol # B7791001 (Higano) 04/18/2016 - 04/30/2019
Pfizer

Megan Shannon I 235 East 42nd Street I New York, NY 10017
A Phase 1 Study to Evaluate the Safety, Pharmacokinetics and Pharmacodynamics of Escalating Doses of a Vaccine-based Immunotherapy Regimen (VBIR) for Prostate Cancer (PF-06753512)
The primary goal is to assess safety and tolerability of increasing dose levels of the prostate cancer vaccine-based immunotherapy regimen (PrCa VBIR) components.
Role: Site PI

Protocol # B030013 (Higano) 03/16/2017-03/15/2022
Hoffman LaRoche
[redacted]
Prasanna Bhende I Covance I 206 Carnegie Center I Princeton, NJ 08540
A Phase IB, Open-Label Study of the Safety and Tolerability of Atezolizumab in Comination with Radium-223 Dichloride in Patients with Castrate-Resistant Prostate Cancer Who Have Progressed Following Treatment with an Androgen Pathway Inhibitor
The primary goals are to assess the safety and tolerability of atezolizumab when given in combination with radium-223 dichloride in patients with mCRPC and to identify a recommended treatment schedule.

Protocol # 9785-CL-0123 (Higano) 03/20/2017 – 05/31/2022
Astellas Pharma Global Development, Inc
[redacted]
Courtney Paul (INC Research) | 4800 Falls of Neuse Rd, Suite 600 | Raleigh, NC 27609
A Phase 2 Open-label Extension Study for Subjects With Prostate Cancer Who Previously Participated in an Enzalutamide Clinical Study
The primary goal of the study is to provide access to continued treatment for subjects who are currently participating in an enzalutamide clinical study, sponsored by Astellas or Medivation, for their prostate cancer and who are continuing to derive clinical benefit based on the assessment of the investigator.

CLINICAL TRIAL CONTRACTS - *Pending*

Protocol # CO-338-063 (Higano)
Clovis Oncology, Inc
Anthony Golsorkhi, MD | Clovis Oncology | San Francisco, CA
TRITON3: A Multicenter, Randomized, Open-label Phase 3 Study of Rucaparib versus Physician's Choice of Therapy for Patients with Metastatic Castration-resistant Prostate Cancer Associated with Homologous Recombination Deficiency
The primary goal of the study is to assess the efficacy of rucaparib versus physician's choice of treatment based on radiographic progression free survival (rPFS0 in mCRPC patients with HRD who progressed on prior AR-directed therapy and have not yet received chemotherapy in the castration-resistant setting.

Protocol # MDV3800-06 (Higano)
Medivation, Inc
Rena Ullum (Quintiles) | 4820 Emperor Blvd, Q Plaza Room 895E | Durham, NC 27703
A Phase 2, Open-label, 2-Arm, Response Rate Study of Talazoparib in Men with DNA Repair Defects and Metastatic Castration-Resistant Prostate Cancer who Previously Received Taxane-Based Chemotherapy and Progressed on at Least 1 Novel Hormonal Agent (Enzalutamide and/or Abiraterone Acetate/Prednisone)
The primary goal of the study is to evaluate efficacy, as measured by best objective response rate (ORR).

Protocol # 000108 (Higano)
Ferring Pharmaceuticals
Ashley Underhill (IQVIA) | 4820 Emperor Blvd, Q Plaza Room 895E | Durham, NC 27703
A Multi-Center, Randomized, Assessor-Blind, Controlled Trial Conparing the Occurrence of Major Adverse Cardiovascular Events (MACEs) in Patients with Prostate Cancer and Cardiovascular Disease Receiving Degarelix (GnRH Receptor Antagonist) or Leuprolide (GnRH Receptor Agonist)
The primary goal of the study is to assess the effect of a GnRH receptor antagonist on the risk of occurrents of MACEs as compared to GnRH receptor agonist in patients with prostate cancer and cardiovascular disease.

Protocol # 18-150 (Higano)
Memorial Sloan Kettering Cancer Center/Bayer Pharmaceuticals
Melanie Chen (MSKCC) | 1275 York Ave | New York, NY 10065

Phase III Trial of Docetaxel vs. Docetaxel and Radium-223 for Metastatic Castration-Resistant Prostate Cancer (mCRPC).
The primary goal of the study is to compare overall survival for subjects treated with docetaxel versus subjects treated with docetaxel plus radium-223.

Protocol # eFT508-0009 (Higano)
eFFECTOR Therapeutics
Angela White (Medpace) | 5375 Medpace Way | Cincinnati, OH 45240
A Phase 2 Non-randomized Open-label Study Examining the Effect of eFT508 in Patients with Advanced Castrate-resistant Prostate Cancer (CRPC).
The primary goal of the study is to assess the anti-tumor response of eFT508 in advanced CRPC.

GRANTS - *Prior*

W81XWH-09-1-0144 (Higano) 12/25/2014 - 09/29/2017
DOD Prostate Cancer Research Program
USA Med Research Acq Activity
Dana Herndon | 820 Chandler St | Fort Detrick, MD 21702-5014
Prostate Cancer Clinical Trials Consortium – Member Site
The Department of Defense provides funding for infrastructure to participate as a clinical site in the Prostate Cancer Clinical Trials Consortium.
Role: Clinical Site PI

W81XWH-BAA-11-1 (Basch) 11/06/2013 - 2/28/2017
UNC-Chapel Hill (DoD flow through)
Mark Kramer | 450 West Drive, CB 7295 | Chapel Hill, NC 27599
DOD Prostate Cancer Research Program: Observational Longitudinal Study of Pain in Men with Metastatic Castrate-Resistant Prostate Cancer
The primary goal is to estimate the proportion of pain palliation responders and the proportion experiencing pain progression as measured by items from the Brief Pain Inventory (BPI) among patients with metastatic castrate-resistant prostate cancer starting systemic therapy.
Role: Site PI

W81XWH-09-1-0144 (Higano) 04/01/2009-12/31/2014
DOD Prostate Cancer Research Program
USA Med Research Acq Activity | Dana Herndon | 820 Chandler St
Fort Detrick, MD 21702-5014
Prostate Cancer Clinical Trials Consortium – Member Site
The Department of Defense provides funding for infrastructure to participate as a clinical site in the Prostate Cancer Clinical Trials Consortium.
Role: Clinical Site PI

U19 AT-006028-03 (Standish) 09/29/2010-08/31/2013
Bastyr/UW Oncomycology Research Center
Bastyr University | Marie Kirkman | 14500 Juanita Dr NE, Room 459 | Seattle, WA 98028-4966
Project 2 (Higano/Wenner):
Enhancing innate immunity by combining PSK with docetaxel in prostate cancer
The primary goal of this phase 1 study is to establish the MTD of PSK alone and in combination with docetaxel and to study the immune effects of each alone and in combination.
Role: Project 2 Co-PI

R01 CA 120933 (Cherrier) 08/07/2007-5/31/2013
NIH/NCI
Assessment of Cognitive and Mood Effects from ADT in Men with Prostate Cancer
The primary goal of this project is to assess the affects of androgen deprivation therapy on mood, information processing, and quality of life

Role: Co-Investigator

P50 CA 097186-06 (Nelson) 09/14/2007-8/31/2012
Fred Hutchinson Cancer Research Center (NIH/NCI flow through) [redacted]
Jill Lauson | 1100 Fairview Ave N | Seattle, WA 98109
Pacific Northwest Prostate Cancer SPORE
Clinical Core D (Higano)
The major goals of this project are to design and execute clinical trials relevant to SPORE projects, to support and enhance the CAISIS clinical data repository, and to support and engage the SPORE Advocacy Committee in SPORE activities in the Pacific Northwest.
Role: Director Clinical Core D

P50 CA 097186 (Lange) 09/01/02-08/31/07
NIH/NCI [redacted]
Pacific Northwest Prostate Cancer Specialized Program of Research Excellence (SPORE)
The main goal of this project is to understand the molecular biology of prostate cancer through all stages of its progression. Focus will be on analyzing gene and protein expression in the entire spectrum of prostate tumors, from those clinically localized and slow-growing to those advance and highly aggressive. The major goals of Core E are to establish a unified database to serve as a clinical data repository, design and execute clinical trials relevant to SPORE projects, and to support and engage the SPORE Advocacy Committee in SPORE activities in the Pacific Northwest.
Role: Co-investigator and Director Clinical Core E (Higano)

CLINICAL TRIAL CONTRACTS - Prior

Protocol # S-3100-1-01 (Higano) 06/27/2007-05/31/2018
Medivation, Inc. [redacted]
Herb Waddell | 55 Hawthorne Street | San Francisco, CA 94105
A Phase I Open-Label Dose-Escalation Safety and Pharmacokinetic Study of MDV3100 in Patients with Castration-Resistant Prostate Cancer
The primary goal is to determine the safety and tolerability profile of MDV3100, including the dose-limiting toxicities (DLTs), and the maximum tolerated dose (MTD; if possible) when administered orally to subjects with castration-resistant prostate cancer.
Role: Site PI

Protocol # P10-3 (Higano) 04/25/2012 - 07/31/2017
Dendreon Corporation [redacted]
Mark Frohlich, MD/Chief Medical Officer | 1301 2nd Ave, Ste 3200 | Seattle, WA 98101
A Registry of Sipuleucel-T Therapy in Men with Advanced Prostate Cancer
The primary goal is to further quantify the risk of cerebrovascular events (CVEs) following sipuleucel-T therapy for all subjects.
Role: Site PI, Member Steering Committee

Protocol # DST4964g (Higano) 06/01/2012 - 03/31/2017
Genentech, Inc [redacted]
Daniel Maslyar | 1 DNA Way | South San Francisco, CA 94080
A Phase I, Open-Label Study of the Safety and Pharmacokinetics of Escalating Doses of DSTP3086S in Patients with Metastatic Castration-Resistant Prostate Cancer.
The primary goals are to evaluate the safety and tolerability of every-3-week administration and of weekly administration of DSTP3086S to patients with CRPC, and; to determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of every-3-week administration and of weekly administration of DSTP3086S to patients with CRPC, and; to identify the recommended Phase II dose of every-3-week administration and of weekly administration of DSTP3086S (at or below the MTD) in patients with CRPC.
Role: Site PI

Protocol # BC1-10 (Higano) 07/30/2012 - 09/30/2016
Algeta ASA
Kari Lyseng | Kjelsaveien 172 A | NO 0411 Oslo | NORWAY
A Phase I/IIa Study of Safety and Efficacy of Alpharadin with Docetaxel in Patients with Bone Metastases from Castration-Resistant Prostate Cancer
The primary goals are to establish a recommended dose of Alpharadin to be used with docetaxel, and; to investigate safety and explore efficacy of the recommended dose of Alpharadin used with the standard treatment regimen of docetaxel in patients with bone metastases from castration resistant prostate cancer, and; to evaluate the feasibility of patient self-reporting of pain intensity and analgesic use via an interactive voice response (IVR) system.
Role: Site PI, member phase 1 working group

Protocol # P07-2 (Higano) 09/10/2010 - 05/31/2016
Dendreon Corporation
Jovine Umail | 1301 Second Ave, Ste 3200 | Seattle, WA 98101
A Randomized, Multicenter, Single Blind Study in Men with Metastatic Androgen Independent Prostate Cancer to Evaluate Sipuleucel-T Manufactured with Different Concentrations of PA2024 Antigen
The primary goal is to compare the cumulative CD54 upregulation ratio between each of the cohorts.
Role: Site PI

Protocol # ARN-509-001 (Higano) 11/01/2011 - 01/28/2016
Aragon Pharmaceuticals, Inc
Rich Heyman | 12780 El Camino Real #301 | San Diego, CA 92130
An Open-Label, Phase 1/2 Safety, Pharmacokinetic, and Proof-of-Concept Study of ARN-509 in Patients with Progressive Metastatic Castration-Resistant Prostate Cancer
The primary goal of Phase 1 is to assess the safety of ARN-509 in patients with progressive advanced castration-resistant prostate cancer (CRPC), and determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of ARN-509 that leads to a dose limiting toxicity (DLT) in a maximum of 30% of patients.
The primary goal of Phase 2 is to determine PSA response at 12 weeks according to PCWG2 criteria.
Role: Site PI

Protocol # XRP6258-CABAZL06056 (Higano) 12/23/2013 - 01/29/2016
Sanofi US Services Inc
Debra Dawson | 55 Corporate Drive | Bridgewater, NJ 08807
Phase II Trial to Evaluate Benefit of Early Switch from First-Line Docetaxel/Prednisone to Cabazitaxel/Prednisone and the Opposite Sequence, Exploring Molecular Markers and Mechanisms of Taxane Resistance in Men with Metastatic Castration-Resistant Prostate Cancer (mCRPC) Who Have Not Received Prior Chemotherapy
The primary goal is to explore the benefit of an early switch from docetaxel/prednisone to cabazitaxel/ prednisone in men with mCRPC who do not achieve _30% prostate-specific antigen (PSA) decline from baseline by cycle 4 with the initial docetaxel treatment (in comparison with historical control of patients who were treated with docetaxel and did not switch).
Role: Site PI

Protocol # P11-4 (Higano) 09/06/2012 - 04/14/2015
Dendreon Corporation
Mark Frohlich, MD/Chief Medical Officer | 1301 2nd Ave, Ste 3200 | Seattle, WA 98101
Immune Monitoring Protocol in Men with Prostate Cancer Enrolled in a Clinical Trial of Sipuleucel-T
The primary goal is to evaluate the immune response induced by sipuleucel-T.
Role: Site PI

Protocol # C14009 (Higano) 08/18/2010 - 03/31/2015
Millennium Pharmaceuticals, Inc.
Laurie LoBue | 40 Landsdowne Street | Cambridge, MA 02139
A Randomized Phase 2 Study of Docetaxel/Prednisone with or without MLN8237, a Novel Aurora A Kinase Inhibitor, in Patients with Castration-Resistant Prostate Cancer Preceded by a Phase 1 Dose-Escalation

The primary goals are to assess the safety and tolerability of MLN8237 administered in patients with solid tumors, including patients with CRPC who are eligible to receive treatment with docetaxel and to determine the recommended dose and schedule of the combination regimen of MLN8237 and docetaxel applicable to future development in phase 2 studies.
Role: Site PI

Protocol # OGX-011-11 (Higano) 08/04/2011 - 12/31/2014
Teva Pharmaceutical Industries
Shawn T Conahan, PhD | 425 Privet Road | PO Box 1005 | Horsham, PA 19044-8005
A Randomized Phase 3 Study Comparing Standard First-Line Docetaxel/Prednisone to Docetaxel/Prednisone in Combination with Custirsen (OGX-011) in Men with Metastatic Castrate Resistant Prostate Cancer
The primary goal is to ascertain whether the survival time distribution for patients randomized to the investigational arm is consistent with longer survival as compared to patients randomized to the control arm.
Role: International Co-PI

Protocol # OGX-11-11 CTC (Higano) 01/19/2012 - 11/3/2014
Teva Pharmaceutical Industries, Ltd
Finance Manager – R&D Division | Industrial Zone, Kiryat Nordau | Netanya | ISRAEL
Enumeration of Circulating Tumour Cells in Patients Enrolled in Protocol OGX-011-11
The primary goals are to enumerate CTC5 at baseline and cycle 2 and 4 in CRPC patients enrolled to Study Protocol OGX-O11-11, and; to demonstrate that the addition of OGX-O1 1 increases the frequency and magnitude of CTC count falls, and; to confirm that CTC count falls associate with overall survival benefit meeting criteria for surrogacy.
Role: Site PI

Protocol #XL 184-203 (Higano) 05/06/2011 - 05/06/2014
Exelixis, Inc.
Pamela A Simonton | 170 Harbor Way | PO Box 511 | South San Francisco, CA 94083-0511
A Randomized Discontinuation Study of XL 184 Subjects with Advanced Solid Tumors
The primary goal is to evaluate the efficacy of cabozantinib (XL184) in subjects with advanced solid tumors
Role: Site PI

Protocol # OGX-011-11SP (Higano) 04/16/2012 - 04/15/2013
Teva Pharmaceutical Industries, Ltd
Shawn T Conahan, PhD | 425 Privet Road | PO Box 1005 | Horsha, PA 19044-8005
Pharmacokinetic and Cardiac Monitoring Study Supplement to Protocol OGX-011-11: A Randomized Phase 3 Study Comparing Standard First-Line Docetaxel/Prednisone to Docetaxel/Prednisone in Combination with Custirsen (OGX-011) in Men with Metastatic Castrate Resistant Prostate Cancer
The primary goals are to determine if custirsen alone or if co-administered with docetaxel alters ECG intervals and morphology with special emphasis on changes in the QTcF interval duration, and; to explore if co-administration of docetaxel and custirsen alters the pharmacokinetics of custirsen, and; to explore if co-administration of docetaxel and custirsen alters the pharmacokinetics of docetaxel, and; to explore the urinary metabolites of custirsen.
Role: Site PI

Protocol # OGX-011-10 (Higano) 11/01/2010 - 04/04/2013
OncoGenex Technologies
Scott Cormack | 400-1001 West Broadway | Vancouver, BC V6H 4B1 | CANADA
A Randomized, Placebo-Controlled, Double-Blind, Phase 3 Study Evaluating the Clinical Benefit of Adding Custirsen to Docetaxel Retreatment/Prednisone as an Option for Second-Line Therapy in Men with Castrate Resistant Prostate Cancer.
The primary goal is to ascertain whether the investigational arm has a greater proportion of patients with durable pain palliation as compared to the control arm.
Role: Site PI

Protocol # CC 055511 (Higano) 06/18/2008 - 12/31/2012
University of California San Francisco
Alice Chin | 1600 Divisadero St, Box 1770 | San Francisco, CA 94115

A Randomized Phase II Study of Intermittent Chemotherapy or Intermittent Chemotherapy with Maintenance GM-CSF in Patients with Previously Untreated Metastatic Hormone Refractory Prostate Cancer

The primary goal is to determine time to disease progression while receiving chemotherapy (i.e. time to chemotherapy resistance) for both arms (intermittent docetaxel/prednisone with or without maintenance GM-CSF).

Role: Site PI

Protocol # CURC/CUOG AVIAS-0601 (Higano) 04/05/2007 - 11/30/2012

Canadian Urology Research Consortium

[redacted]

Patty Djan | Sunnybrook and Women's College Health Sciences Centre | 2075 Bayview Avenue, Ste A3 04 | Toronto, ON M4N 3M5 | CANADA

Multicentre, Double-Blind Study Ccomparing 0.5mg Dutasteride vs Placebo Daily in Men Receiving Intermittent Androgen Ablation Therapy for Prostate Cancer

The primary goal is to assess the effect of therapy with repeat oral once daily dosing of dutasteride 0.5mg on the length of the off treatment interval in men receiving intermittent androgen ablation therapy for localized prostate cancer.

Role: Site PI

Protocol # CRPC2 (Higano) 12/16/09 - 8/30/2012

Medivation, Inc.

[redacted]

Contract Administration | 201 Spear St, 3rd fl | San Francisco, CA 94105

A Multinational Phase 3, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Oral MDV3100 in Patients with Progressive Castration-Resistant Prostate Cancer Previously Treated with Docetaxel-Based Chemotherapy

The primary goal is to determine the benefit of MDV3100 as compared to placebo as assessed by overall survival.

Role: Site PI

Protocol # IMCL CP13-0603 (Higano) 07/19/2007 - 06/30/2012

ImClone Systems, Inc.

[redacted]

John Blanchette | 33 ImClone Dr | Branchburg, NJ 08876

Phase II Single Arm, Open-Label Study of IMC-A12 in Asymptomatic, Chemotherapy-Naïve Patients with Metastatic Androgen-Independent Prostate Cancer.

The primary goals are to determine the composite time to disease progression for chemotherapy-naive patients with asymptomatic, metastatic androgen-independent prostate cancer (AIPC) treated with IMC-A12 every other week, and; to determine the safety and pharmacokinetic profile of IMC-A12 administered at a dose of 20 mg/kg every 3 weeks in chemotherapy-naive patients with asymptomatic, metastatic AIPC.

Role: Site PI

Protocol #IMCL CP18-0601A (Higano) 12/04/2008 - 06/17/2012

ImClone Systems, Inc.

[redacted]

Clinical Affairs Department | 33 ImClone Dr | Branchburg, NJ 08876

A Phase 2, Multicenter, Randomized Study of IMC-A12 or IMC-1121B plus Mitoxantrone and Prednisone in Metastatic Androgen-Independent Prostate Cancer Following Disease Progression on Docetaxel-Based Chemotherapy

The primary goal is to determine a composite progression-free survival (PFS) associated with the treatment regimen in each arm of the study.

Role: Site PI

Protocol # CMCS110A2101 (Higano) 01/15/2009 - 01/15/2012

Novartis

[redacted]

Wanda Ruiz, PhD | 59 Route 10 | East Hanover, NJ 07936-1080

A Phase I/II Open-Label Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of MCS110 in Patients with Prostate Cancer and Bone Metastases

The primary goal of the dose escalation phase is to determine the maximum-tolerated dose (MTD) or optimal biological dose (OBD) and to characterize dose limiting toxicity (DLT) of escalating doses of MCS110 administered as an IV infusion every 2 weeks on a 28-day cycle in patients with asymptomatic castrate-resistant prostate cancer with bone metastases who have not received any bisphosphonates in the 12 months prior to enrollment.

The primary goal of the dose expansion phase is to assess the effect of MCS110 administered as an IV infusion every 2 weeks on a 28-day cycle on bone resorption marker uNTx in patients with asymptomatic castrate-resistant prostate cancer with bone metastases who have not received any bisphosphonates in the 12 months prior to enrollment.

Role: Site PI

Protocol # IMCL CP13-0501 (Higano) 08/19/2005 - 12/31/2011
ImClone Systems, Inc
Tom Perone | 33 ImClone Dr | Branchburg, NJ 08876
A Phase 1 Study of Weekly Anti-Insulin-Like Growth Factor-1 Receptor (IGF-IR) Monoclonal Antibody IMC-A12 in Patients with Advanced Solid Tumors
The primary goal is to establish the safety profile and maximum tolerated dose (MTD) of the anti-IGF-IR monoclonal antibody IMC-A12 administered weekly in patients with advanced solid tumors who no longer respond to standard therapy or for whom no standard therapy is available.
Role: Site PI

Protocol # AURA-6202-007 (Higano) 02/01/2008 - 12/31/2011
Nerviano Medical Sciences
Elma Ravizza | Viale Pasteur 10 | 20014 Nerviano (MI) | ITALY
A Phase II Study of PHA-739358 in Patients with Metastatic Hormone Refractory Prostate Cancer
The primary goal is to assess the antitumor activity of PHA-739358 administered as IV infusion according to two different dose schedules in metastatic HRPC patients progressing on standard, docetaxel-based, 1st-line chemotherapy for HRPC based on PSA response rate and to select the best dose schedule for further investigation.
Role: Site PI

Protocol # AMG 102-20070611 (Higano) 11/01/2008 - 10/31/2011
Amgen, Inc
Maria Earle | One Amgen Center Drive, MS 28-1-A | Thousand Oaks, CA 91320
A Phase 1b/2 Study to Assess the Safety and Efficacy of AMG 102 in Combination with Mitoxantrone and Prednisone in Subjects with Previously Treated Castrate Resistant Prostate Cancer
The primary goal is to identify safe dose levels of AMG 102, up to 15 mg/kg Q3W, to combine with mitoxantrone and prednisone (MP).
Role: Site PI

Protocol # MDX010-21 (Higano) 02/01/2006 - 02/01/2011
Medarex, Inc
Project Manager | 519 Route 173 West | Bloomsbury, NJ 08804
A Phase I/II, Open-Label, Dose-Escalation Study of MDX-010 Administered Every 3 Weeks for 4 Doses in Patients with Metastatic Hormone-Refractory Prostate Cancer
The primary goal is to determine the safety profile of escalating doses of MDX-010 (hereafter referred to as ipilimumab) with and without a single dose of focal radiotherapy administered every 3 weeks up to 4 times to patients with metastatic hormone-refractory prostate cancer (HRPC).
Role: Site PI

Protocol # D9902 (Higano) 10/01/2003 - 09/30/2010
Dendreon
Mark Frohlich, MD/Chief Medical Officer | 1301 2nd Ave, Ste 3200 | Seattle, WA 98101
A Randomized, Double Blind, Placebo Controlled Phase 3 Trial of Immunotherapy with Autologous Antigen Presenting Cells Loaded With PA2024 (Provenge®, APC8015) in Asymptomatic Subjects With Gleason Sum ≤ 7, Metastatic, Androgen Independent Prostatic Adenocarcinomas
The primary goal is to assess the safety and efficacy of sipuleucel-T in prolonging survival of men with metastatic androgen independent prostate cancer.
Role: Site PI

Protocol # G-0029 (Higano) 08/15/2005 - 08/31/2010
Cell Genesys
Karen Peterson | 500 Forbes Blvd | South San Francisco, CA 94080
A Phase III Randomized, Open-Label Study of CG1940 and CG8711 Versus Docetaxel and Prednisone in Patients with Metastatic Hormone-Refractory Prostate Cancer who are Chemotherapy-Naïve

The primary goal is to compare the duration of survival between the two treatment arms.
Role: Site PI

Protocol # APL-B-011-02 (Higano) 03/01/2006 - 02/28/2010
PharmaMar
Clementina Martinez | Avda. De los Reyes, 1 | Pol. Ind. La Mina-Norte | 28770-Colmenar Viejo | Madrid, Spain
A Phase II, Multicenter, Open-Label, Clinical and Pharmacokinetic Study of Aplidin® as a 3-hour IV Infusion Every 2 Weeks, in Relapsing or Refractory Patients with Androgen-Independent Prostate Adenocarcinoma
The primary goal is to assess the anti-tumor activity of Aplidin® given intravenously over 3-hours every 2 weeks, in patients with castrate metastatic adenocarcinoma of the prostate that have relapsed or progressed after two previous lines of systemic therapy, considering biological agents or chemotherapy as systemic therapy and taking into account that patients must have received prior docetaxel-based chemotherapy.
Role: Site PI