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PRINCIPAL INVESTIGATOR: Heather Cheng, MD, PhD

CONTRACTING ORGANIZATION: University of Washington

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Heather Cheng, MD, PhD

E-Mail: hhcheng@uw.edu

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14. ABSTRACT

Purpose: Participate as an active and productive member of the Prostate Cancer Clinical Trial Consortium (PCCTC) throughout the funding period.
Scope: This is the annual report summarizing the site activities for the University of Washington (UWash) for the funding period 30Sep2020-29Sep2021.
Major Progress: In the last year, UWash was the lead/co-lead site on 7 trials and completed accrual on 1 trials.
Results: UWash accrued 26 patients to PCCTC trials.
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, germline genetics, circulating tumor cells, androgen receptor, biopsy

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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 28 patients (goal 25) to PCCTC trials, 16 patients to therapeutic and 12 patients to non-therapeutic trials. See Appendix 1 for details.
      ii. 11 of 28 patients (actual 39%, goal >5%) accrued during this reporting period were members of disproportionately affected populations.
      iii. Site submitted the following LOIs (3) during the current report period: c21-271, c21-274 and c21-275. In this award period to date (30Sep2017-29Sep2021), 8 LOIs have been submitted and accepted.
      iv. Site participated in 8 PCCTC trials: 1 trial initiated by other PCCTC sites, 1 initiated by UWash with another site, and 6 initiated by UWash. This award period to date, site has participated in 24 PCCTC trials: 7 initiated by other sites, 7 initiated by UWash with other sites, and 10 initiated by UWash.
      v. Site met requirements of timely submission of quality data.
      vi. Dr. Cheng is the Chairperson of the Germline Genetics Working Group, and Dr. Yu is a member of same. 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. Meetings were held virtually due to the COVID19 pandemic. In

addition, Dr. Cheng presented on behalf of the PCCTC/PCF Germline Genetics Working Group at GU ASCO on February 11, 2021.

viii. Coordinator participates in site conference calls. PI and/or co-I and sub-investigators participate in all monthly PI conference calls.

ix. Drs. Cheng, Yu and Schweizer attended the EAB meeting held on June 6, 2021 at virtual ASCO. Dr. Cheng, together with Dr. Channing Paller (Johns Hopkins) presented the PROMISE registry study.

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. Due to the COVID pandemic, the 9th annual meeting was held virtually.

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?**
Continue current activities including opening and accruing patients to new PCCTC trials and proposing new LOIs. Dr. Cheng was awarded a 2020 NCI Cancer Clinical Investigator Team Leadership Award, which supports her efforts to increase clinical trials education and accrual in the UWash cancer consortium catchment region through more effective communication and outreach among community colleagues and patients.

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 for 2022 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.

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.

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**
   The COVID19 pandemic caused delays in opening trials, accruing patients and inaccurate assessment and monitoring during trial conduct. Despite these challenges, we have managed to continue to meet our goals and have effectively and efficiently adapted to changes. We will continue to collaborate with other PCCTC sites with the goal of eliminating deaths from prostate cancer and enhancing the well-being of men experiencing the impact of prostate cancer.

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 (UWash author)

Abstracts:

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.

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

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

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.

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
Project Role:	Principal Investigator (effective 01Jul2020)
Person months worked:	2
Contribution to project:	Responsible for site's overall performance, assures site's goals are being met as outlined in the SOW, participates as a senior PCCTC member and mentor.

Name:	Evan Yu, MD
Project Role:	Co-Principal Investigator
Person months worked:	1
Contribution to project:	Conducts and recruits to PCCTC clinical trials, participates in weekly research and monthly PCCTC protocol meetings, attends face-to-face PCCTC meetings.

Name:	Michael Schweizer, MD
Project Role:	Co-Principal Investigator
Person months worked:	1
Contribution to project:	Conducts and recruits to PCCTC clinical trials, participates in weekly research and monthly PCCTC protocol meetings, attends face-to-face PCCTC meetings.

Name:	Zoya Bauer
Project Role:	Clinical Research Coordinator
Person months worked:	3
Contribution to project:	Tracks trial accruals, LOI submissions, and provides updates to PCCTC. Serves as point person for PCCTC activities. Participates in PCCTC coordinator conference calls. Manages consortium budgets and contract, provides monthly reports, oversees start-up process for PCCTC clinical trials, and post award accounting of the DoD grant. Assists PI and co-PI with preparation and submission of required semi-annual and annual reports.

Name:	Sarah Finkelstein
Project Role:	Operations Support
Person months worked:	2
Contribution to project:	Supports CRC in tracking accruals and LOI submissions. Serves as resource to UWash team with respect to DOD award requirements. Assist PI, co-PI and CRC with preparation and submission of semi-annual and annual reports.

Name:	Colin Sievers
Project Role:	Research Coordinator
Person months worked:	2
Contribution to project:	Research coordinator for UWash PCRP trials. Serves as a resource for the conduct of protocol specified laboratory correlative projects.

Name:	Nathan Conrad
Project Role:	Data Coordinator
Person months worked:	1
Contribution to project:	Set up research charts and work-flow plans, and ensures timely submission of quality data for all UWash PCCTC trials.

Name:	Randall Davis
Project Role:	Budget Startup Specialist
Person months worked:	2
Contribution to project:	Develops site budgets for PCCTC studies, and negotiates amendments based on protocol modifications as needed.

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

30Sep2020-29Sep2021

Table A UWash PCCTC Trials, Open and in Start-Up
(abbreviation mCRPC = metastatic castration resistant prostate cancer)

PCCTC# (UW#)	Trial Title	UWash Accrual Current	Status	Lead	Protocol Specific Lab Projects
c16-169 (UW15030)	A Phase 1 Study… of Escalating Doses of a Vaccine Based Immunotherapy Regimen (VBIR) for Prostate Cancer	0	Closed 02/2021	UWash Duke MSKCC	PK, PD, AChR, PBMC, PSMa & IgG Serology, MDSCa, CTCs,
c19-248 (UW18002)	A Phase I Dose Escalation and Expanded Cohort Study of PF-06821497 in the Treatment of Adult Patients with Relapsed/Refractory Small Cell Lung Cancer (SCLC), Castration Resistant	3	Open	UWash	PK, PD Biomarkers, DNA repair mutations
c20-259 (RG1004978)	A Phase 1, First-in-Human, Dose Escalation Study of JNJ-63898081 in Subjects with Advanced Stage Solid	3	Open	UWash	PK, PD, Biomarkers
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,	8	Open	UWash	
c21-275 (RG1007001)	Durvalumab (MEDI4736) and Olaparib (AZD2281) for treatment of biochemically recurrent prostate cancer in men predicted to have a high	2	Open	UWash	ctDNA, RNA, Tumor Genetic Characteristics (NGS)
	Total Therapeutic accruals:	*16*			
c16-170 (CC9853)	Prostate Cancer Outcomes: An International Registry to Improve Outcomes in Men with Advanced	4	Open	Duke MSKCC DFCI	ctDNA, germline DNA, RNA, exosomes
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	3	Open	UWash	NGS for DNA repair mutations
C21-271 (RG1006494)	Darolutamide Observational Study in non-metastatic castration-resistant prostate cancer patients	5	Open	uWash	
	Total non-therapeutic accruals	*12*			

Appendix 2

Copies of original journal articles

HHS Public Access

Author manuscript

Clin Cancer Res. Author manuscript; available in PMC 2021 April 15.

Published in final edited form as:

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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.

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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.

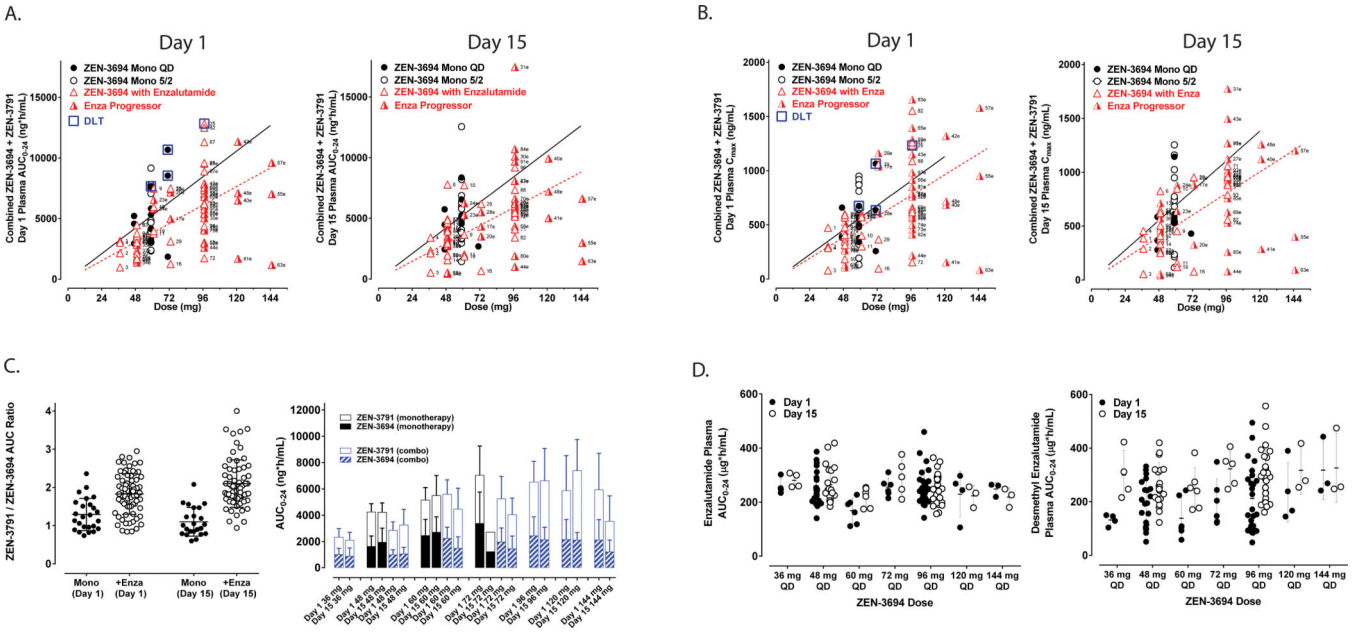

Figure 1. Pharmacokinetic analyses.

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.

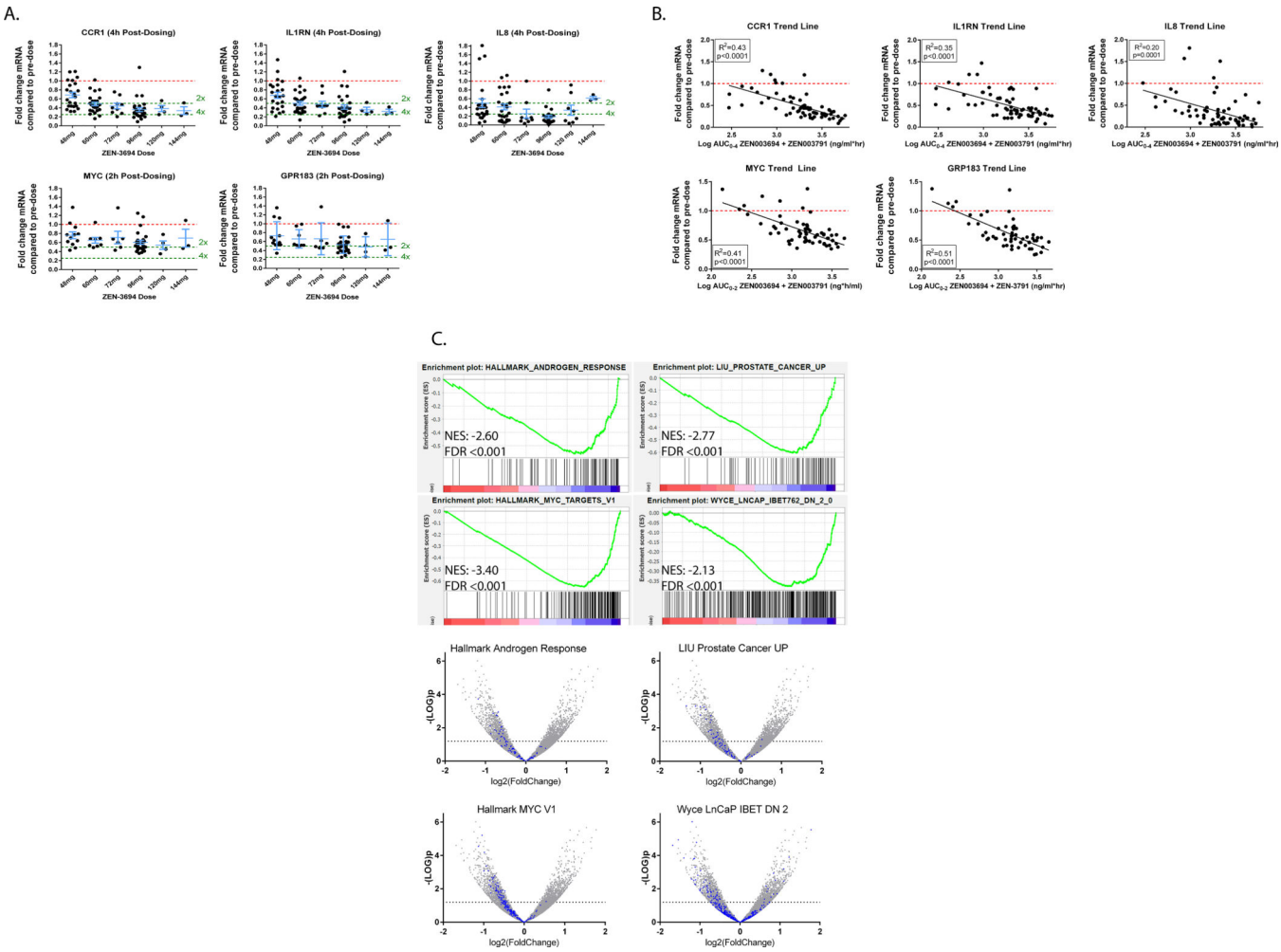

Figure 2. Pharmacodynamic assessments.

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.

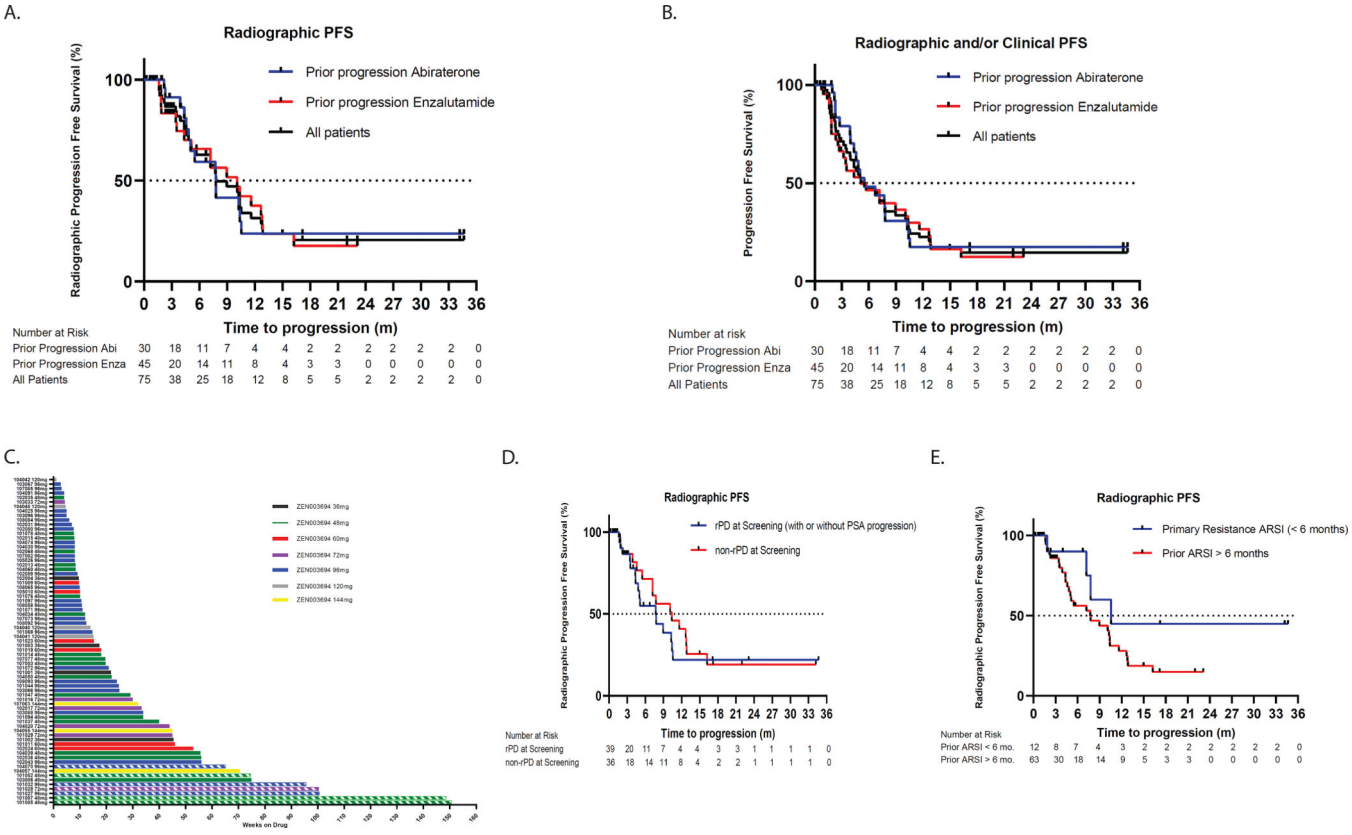

Figure 3. Radiographic progression-free survival and duration of treatment.

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.

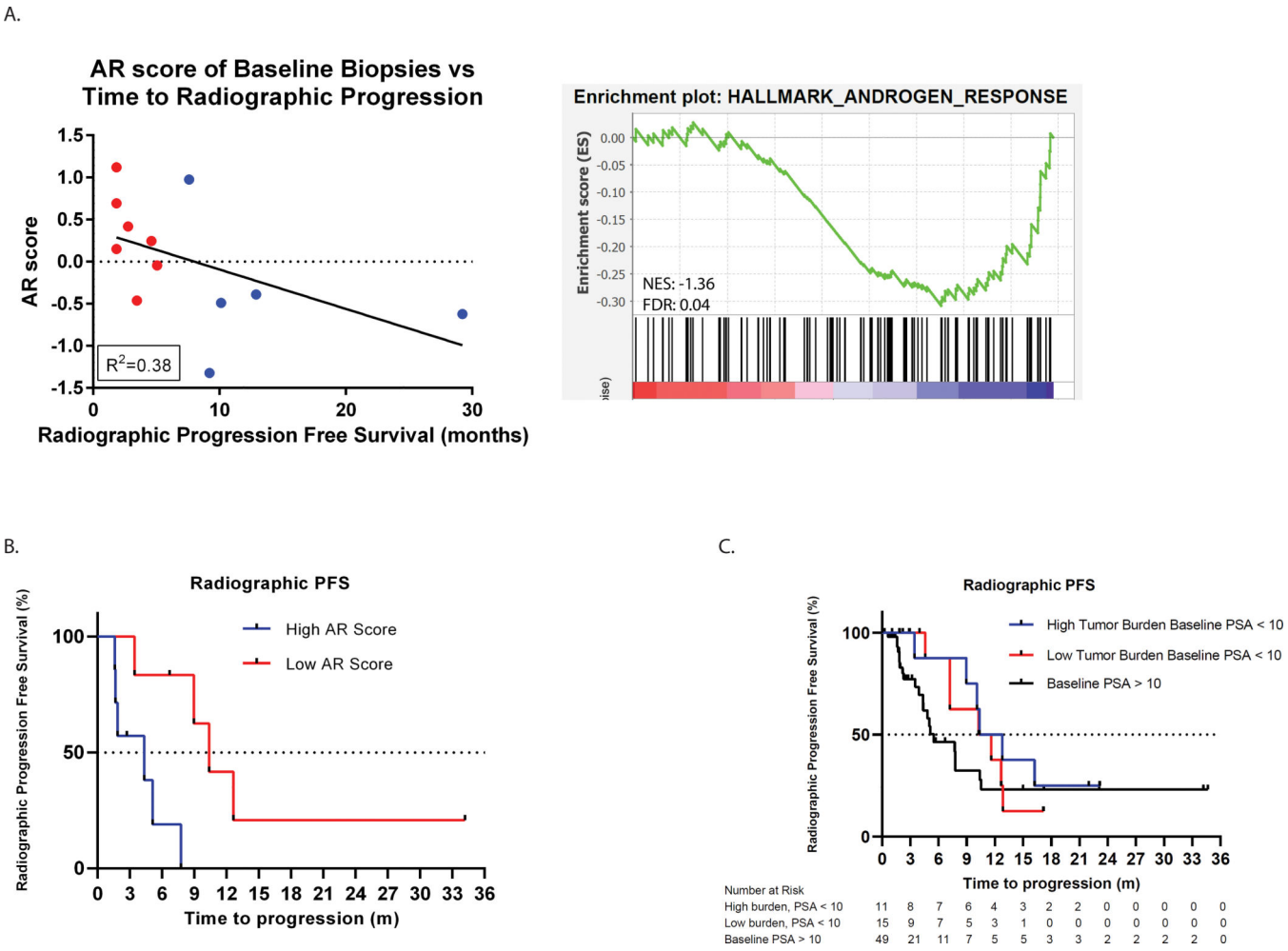

Figure 4. AR signaling score and clinical outcomes

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.

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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.

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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

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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

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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.

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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

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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)

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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.

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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.

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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.

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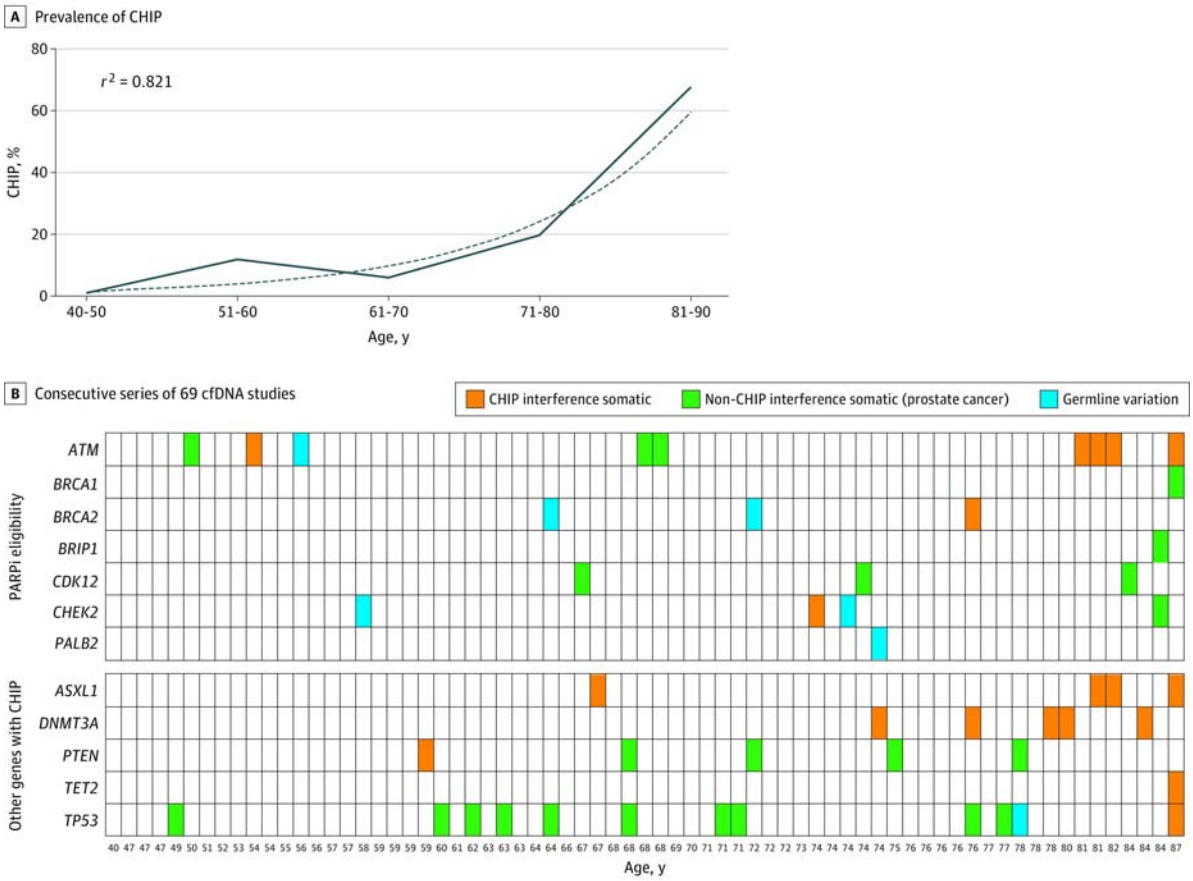
Figures and Tables

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.

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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.

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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.

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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.

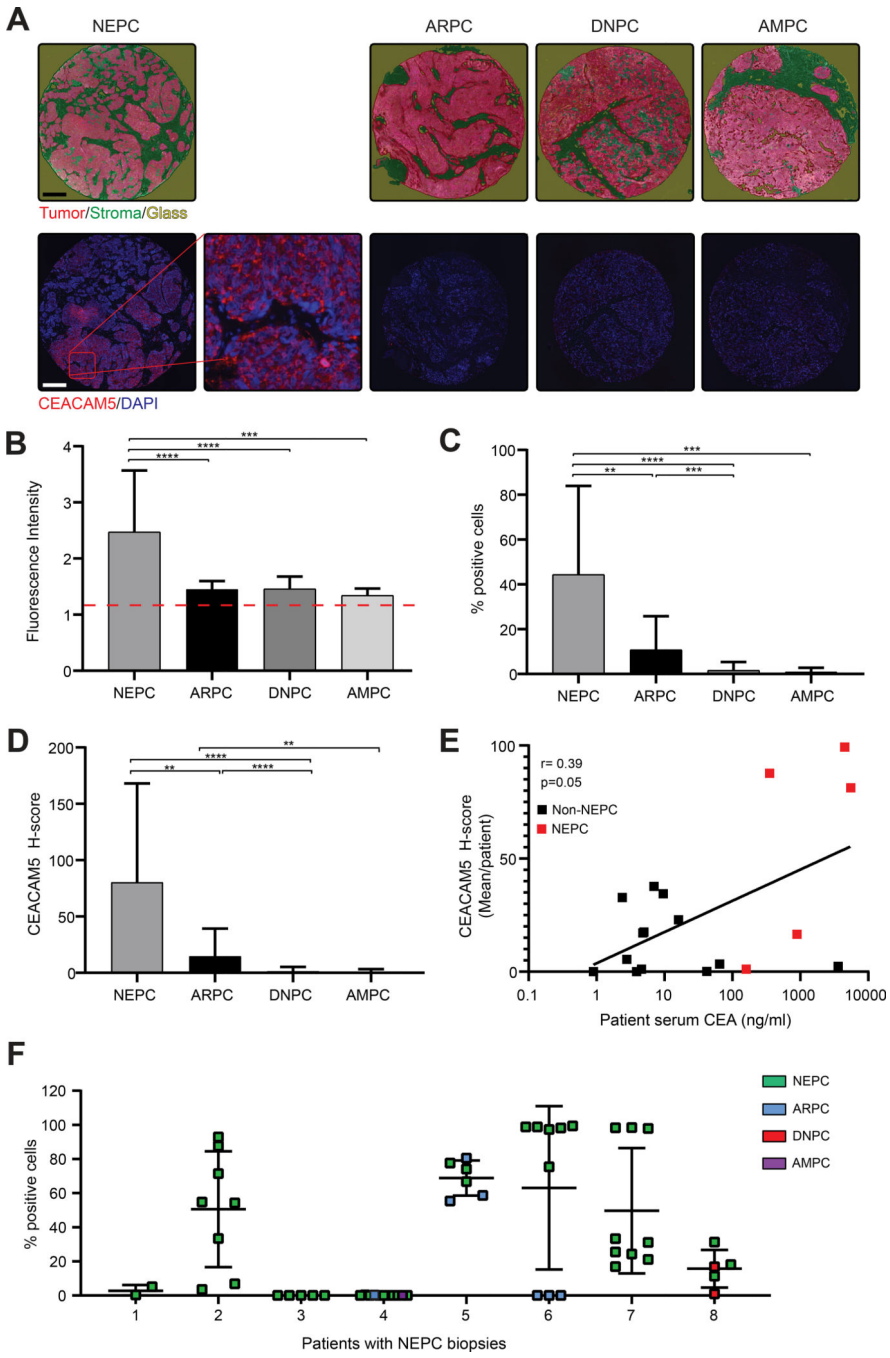

Figure 1. CEACAM5 expression is enriched in the NEPC subtype of mCRPC.

(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.

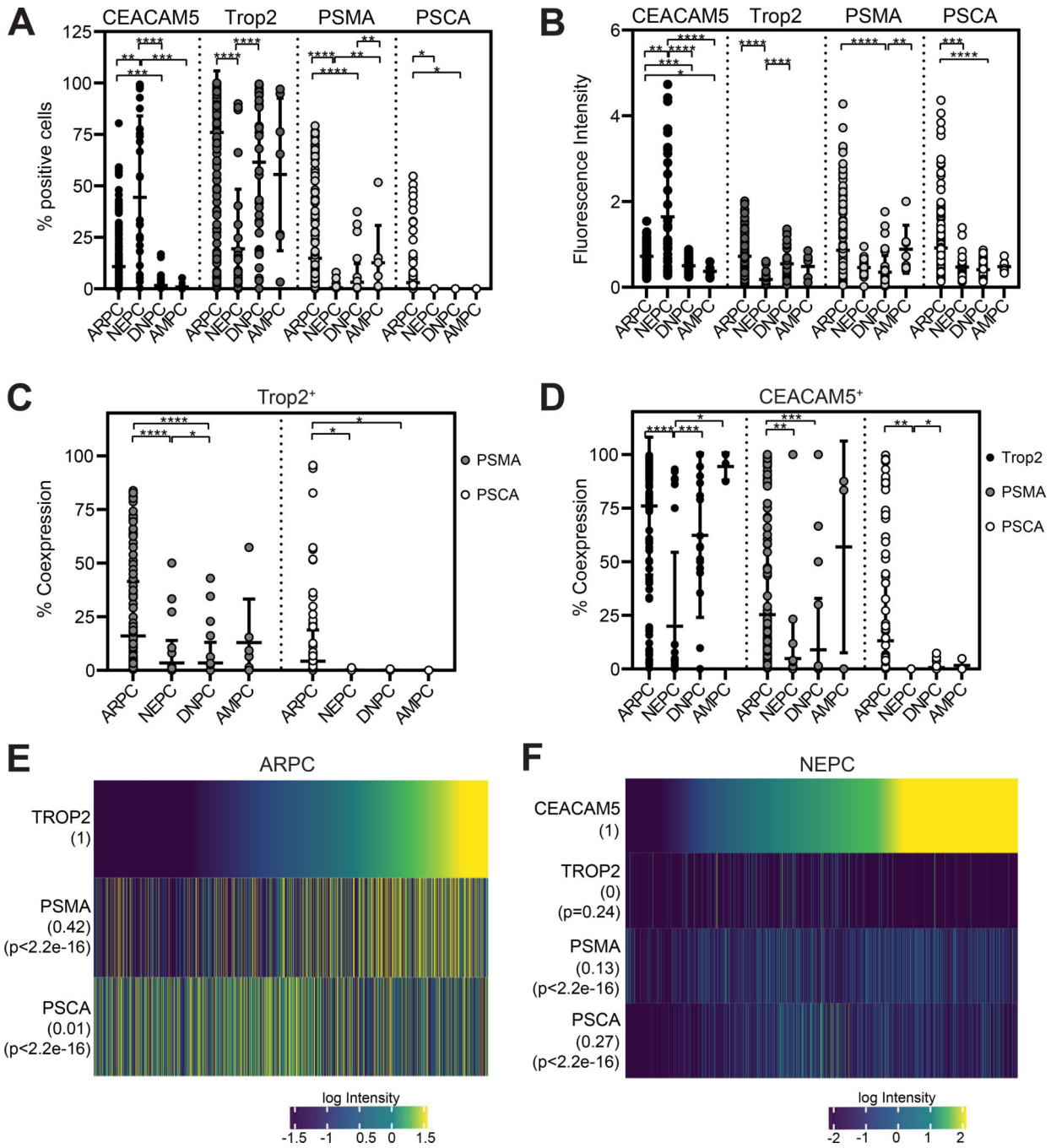

Figure 2. CEACAM5 expression relative to other targetable prostate cancer cell surface antigens.

(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.

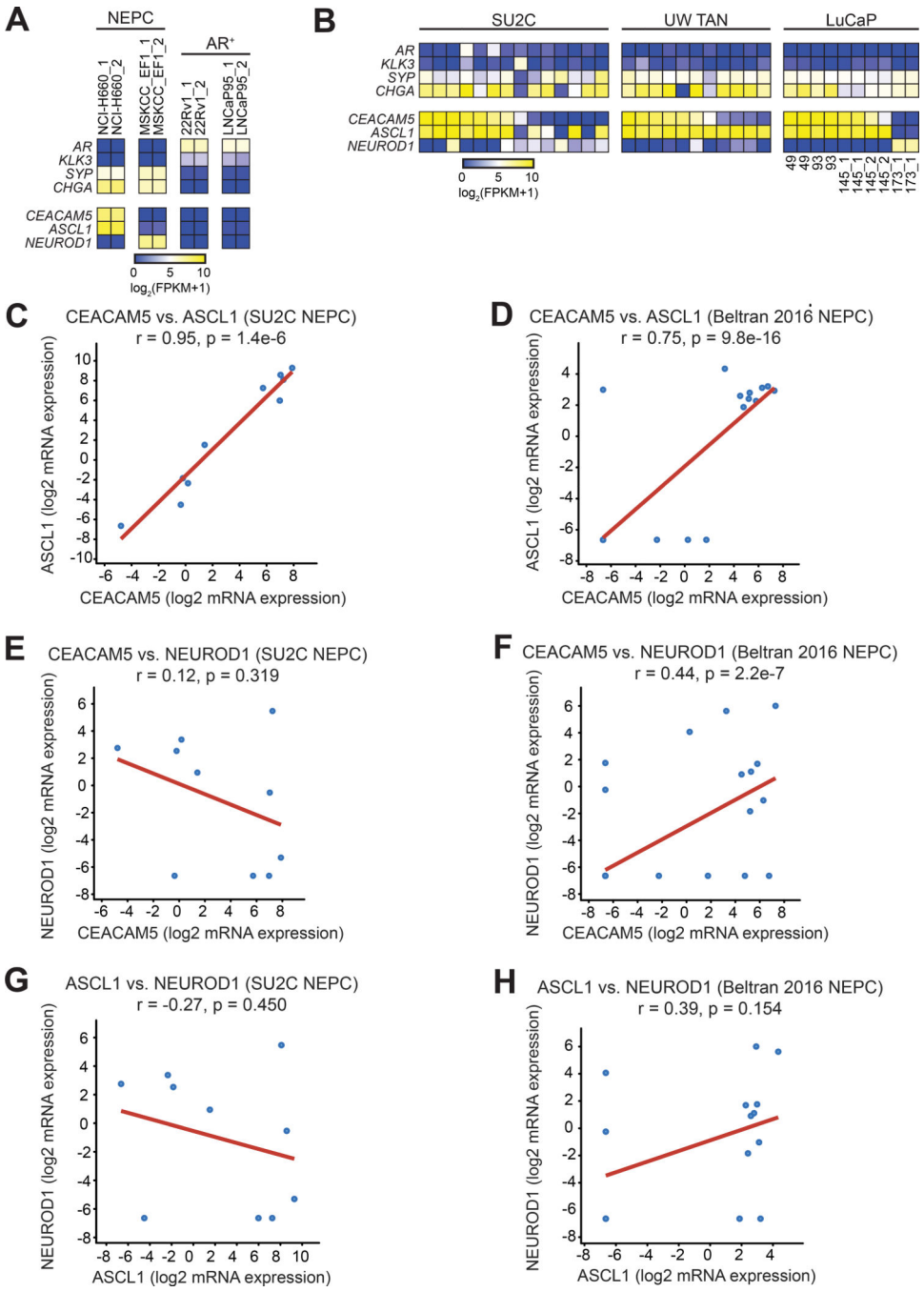

Figure 3. Association of ASCL1 and CEACAM5 expression in NEPC.

(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.

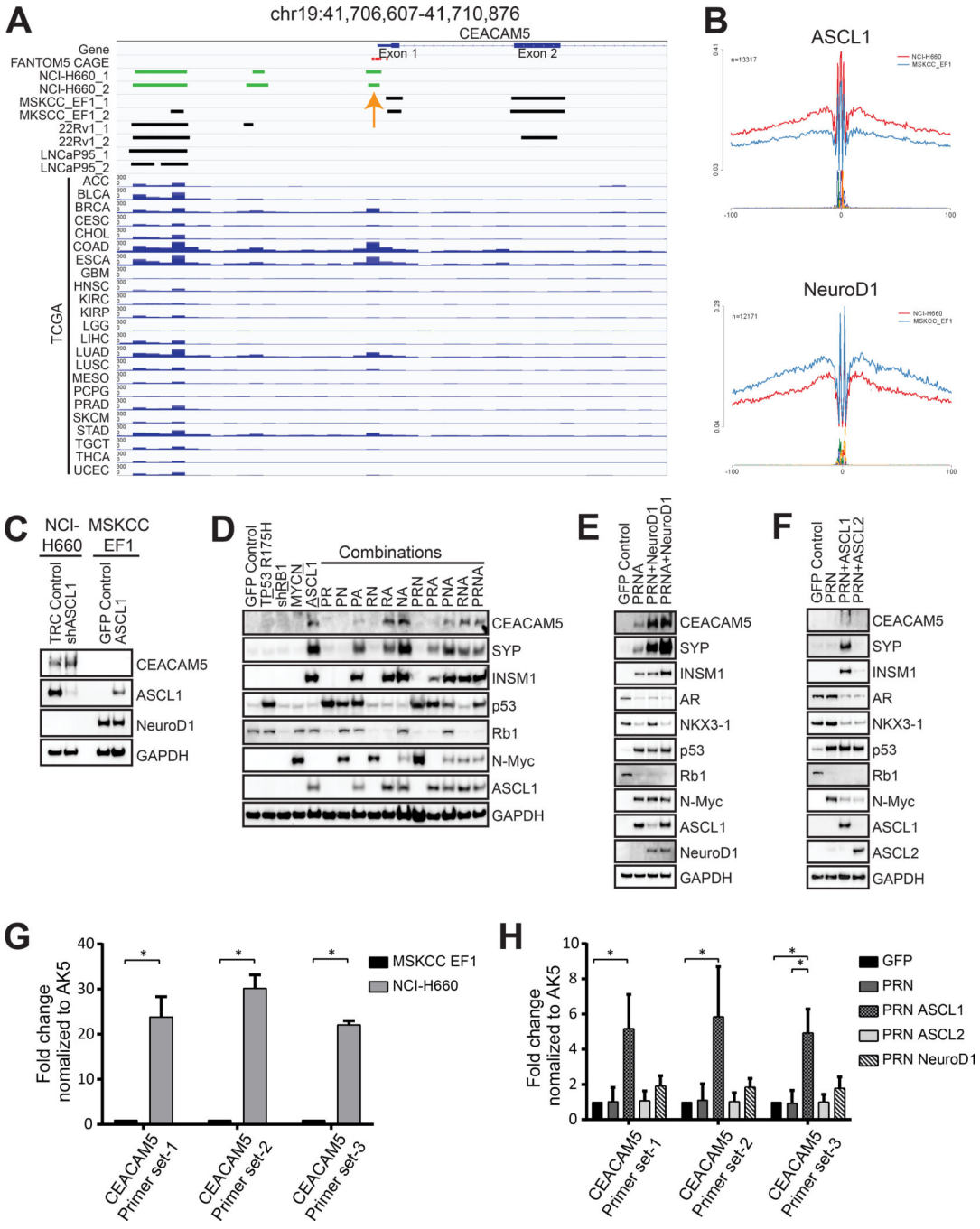

Figure 4. Regulation of CEACAM5 expression during neuroendocrine transdifferentiation.

(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.

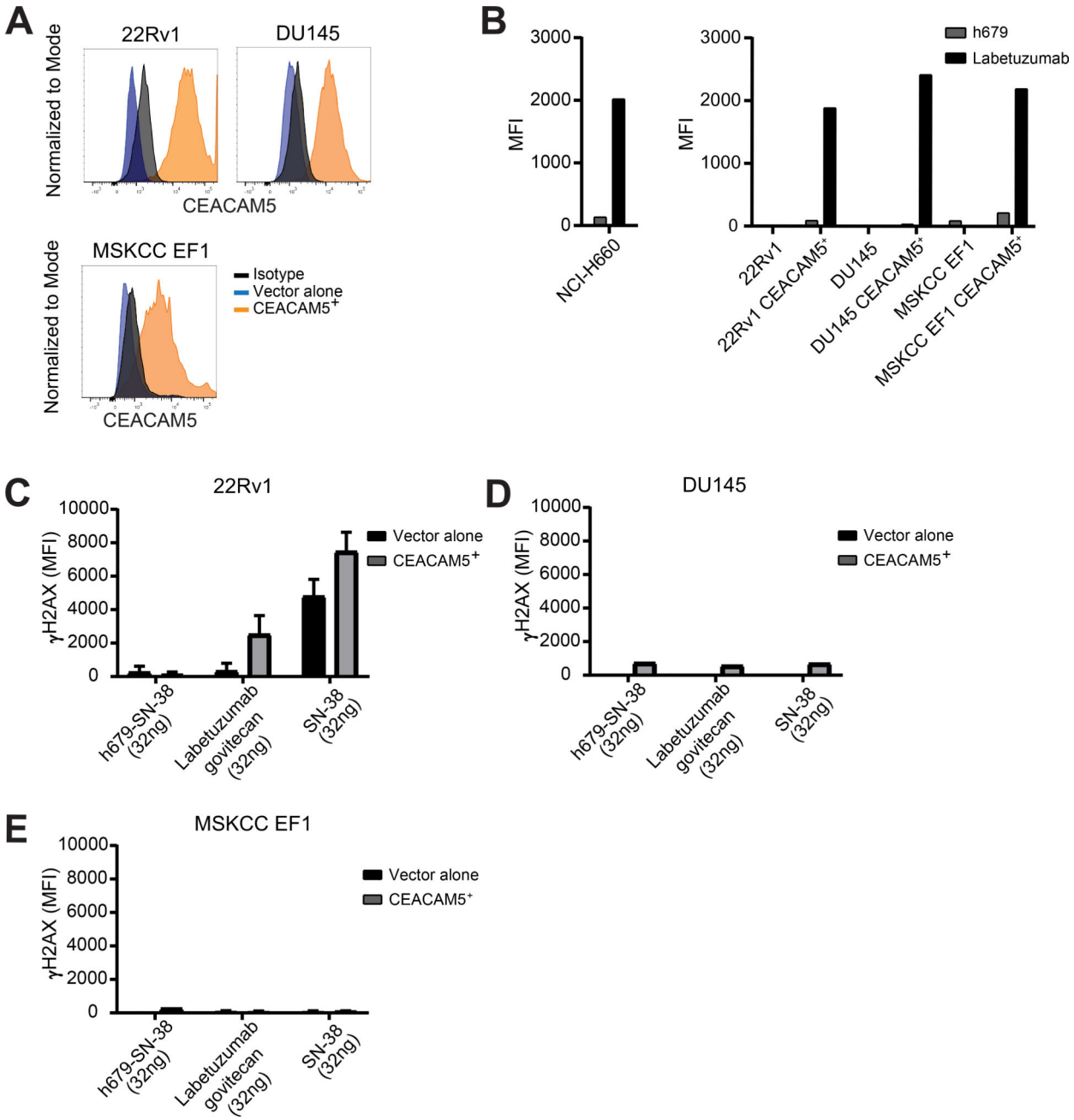

Figure 5. Labetuzumab govitecan induces dsDNA damage in a CEACAM5-specific manner.

(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.

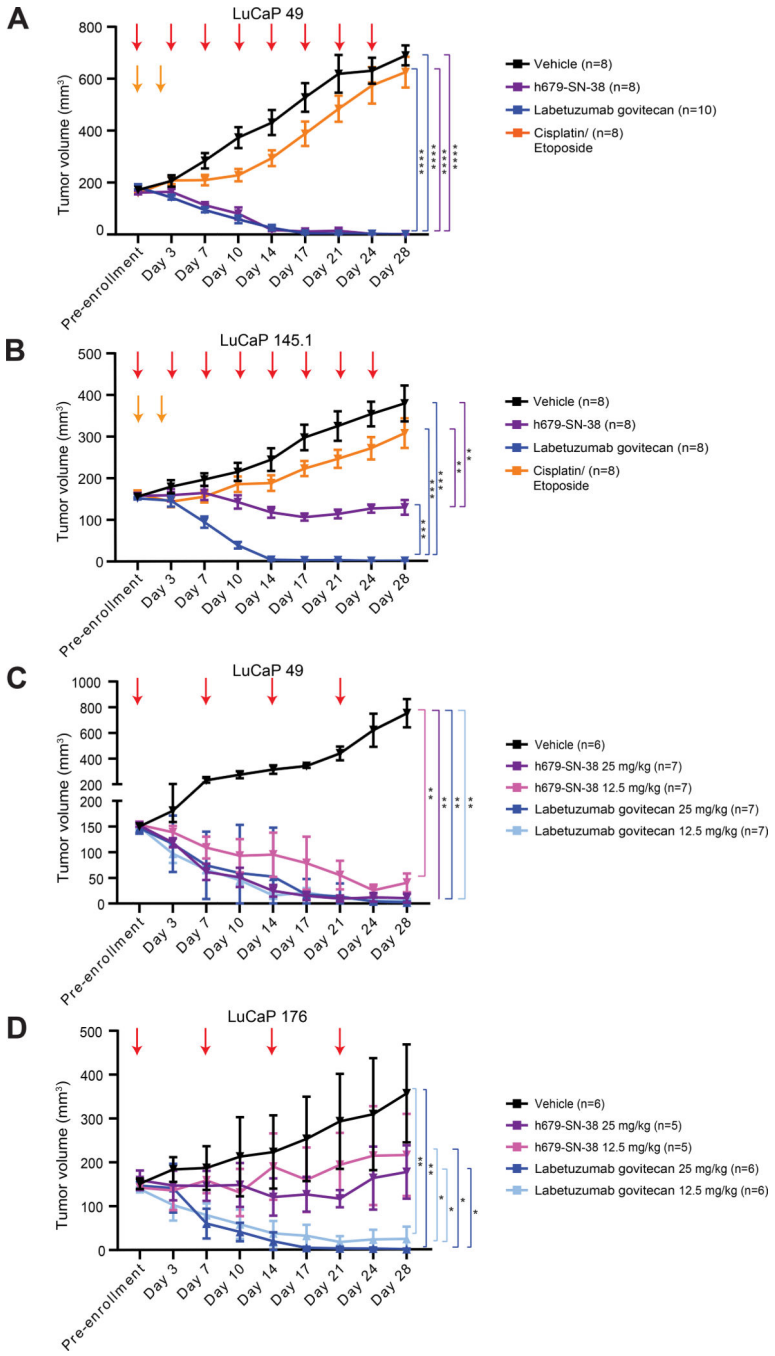

Figure 6. Labetuzumab govitecan eradicates CEACAM5^{+} LuCaP PDXs *in vivo*.

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.

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ASSOCIATED CONTENT

Data Supplement
Protocol

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

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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.

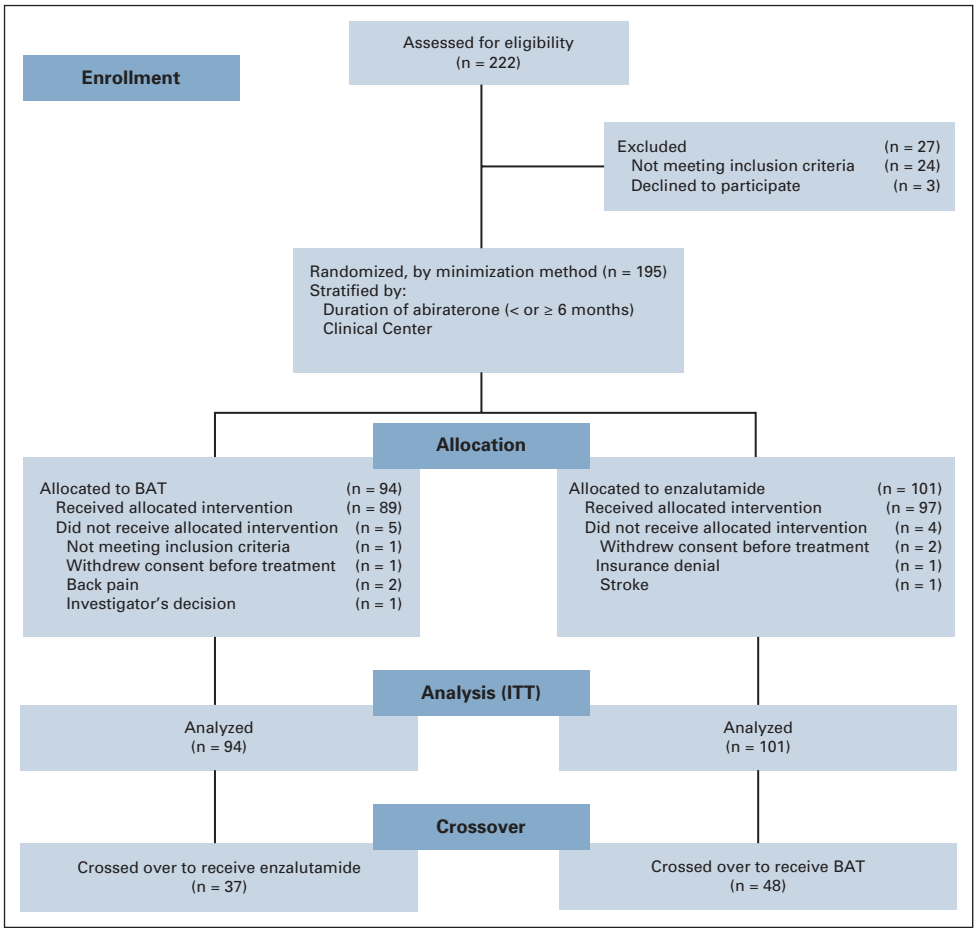

FIG 1. TRANSFORMER CONSORT diagram. BAT, bipolar androgen therapy.

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

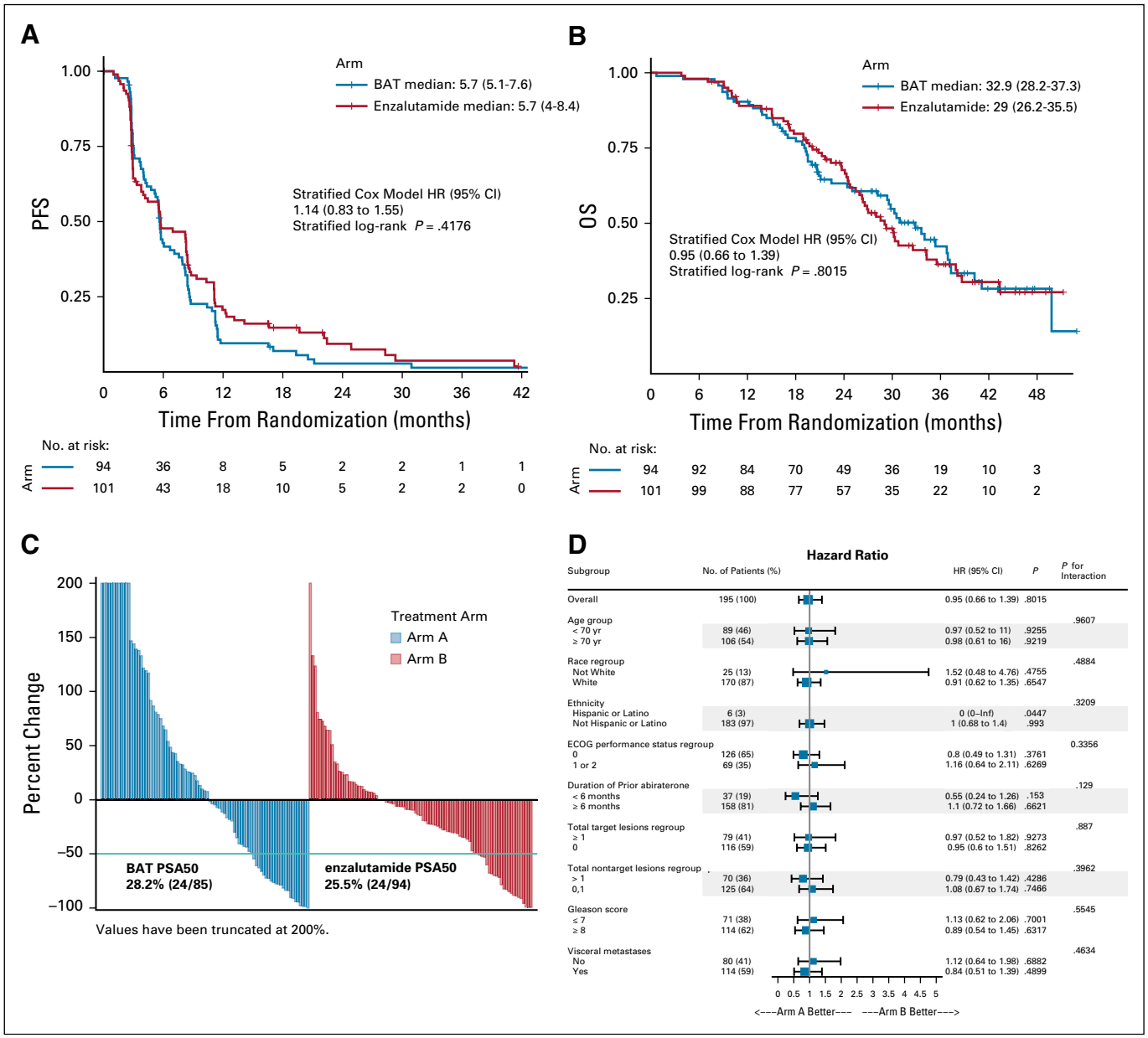

FIG 2. Kaplan-Meier estimates of (A) PFS and (B) OS, (C) waterfall plot of PSA response to initial therapy, (D) subgroup analysis of OS. BAT, bipolar androgen therapy; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; INF, infinity; OS, overall survival; PFS, progression-free survival; PSA, 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

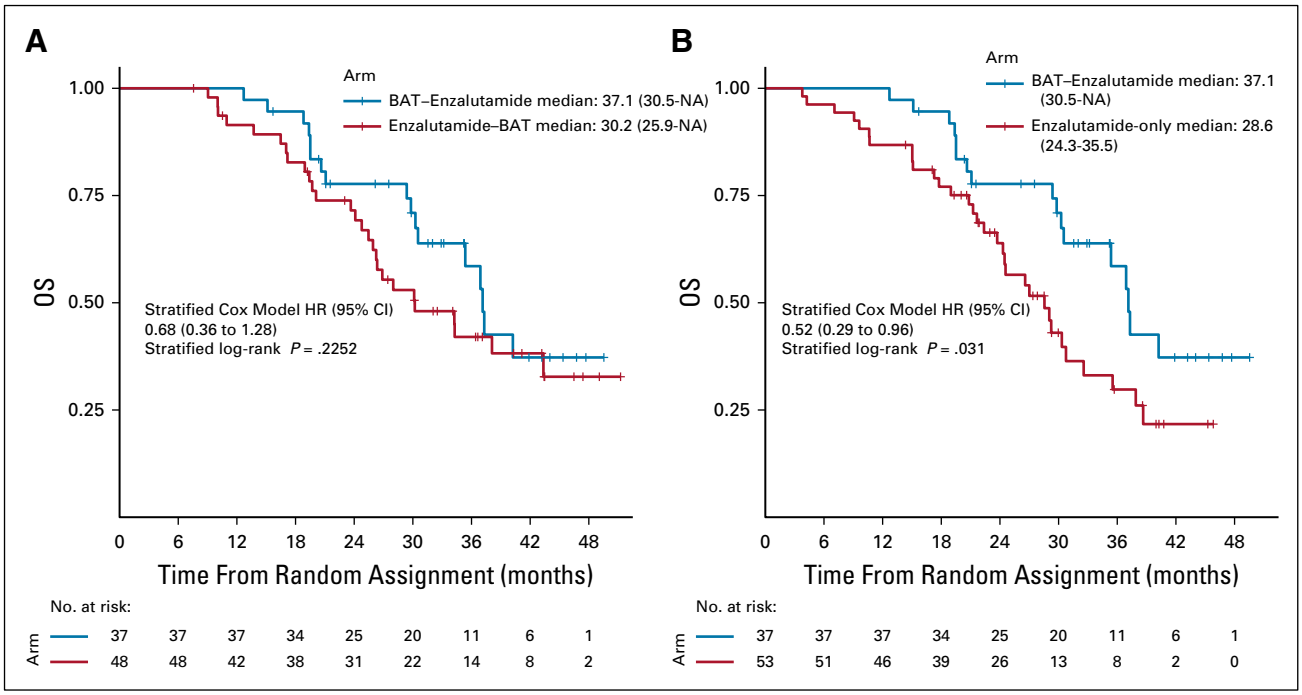

FIG 3. Kaplan-Meier estimates of OS in the crossover population. (A) Comparison of OS in the subset of patients receiving BAT→enzalutamide versus enzalutamide→BAT, after eliminating those who came off study without crossing over. (B) Comparison of OS in the subset of patients receiving BAT→enzalutamide (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%

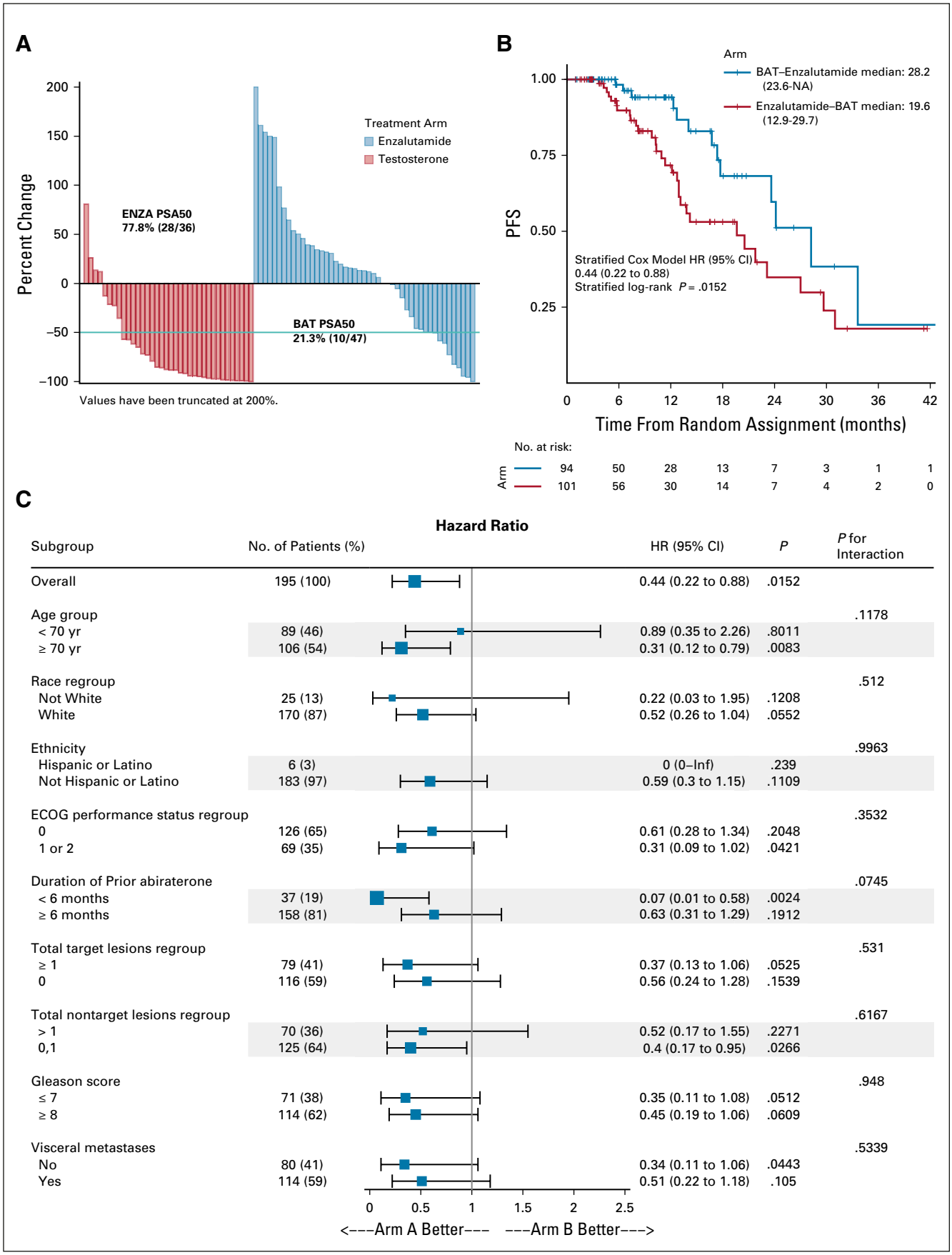

FIG 4. (A) Waterfall plot of PSA response to crossover therapy, (B) Kaplan-Meier estimates of PFS2, (C) subgroup analysis of PFS2. BAT, bipolar androgen therapy; ECOG, Eastern Cooperative Oncology Group; PFS, progression-free survival; PSA, prostate-specific antigen.

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.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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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

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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

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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

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ORIGINAL ARTICLE

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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

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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

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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Platinum Priority – Editorial

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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

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* Division of Medical Oncology, University of Washington, 825 Eastlake Avenue East, Seattle, WA 98109, USA. E-mail address: hhcheng@uw.edu.

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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.

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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.

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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.

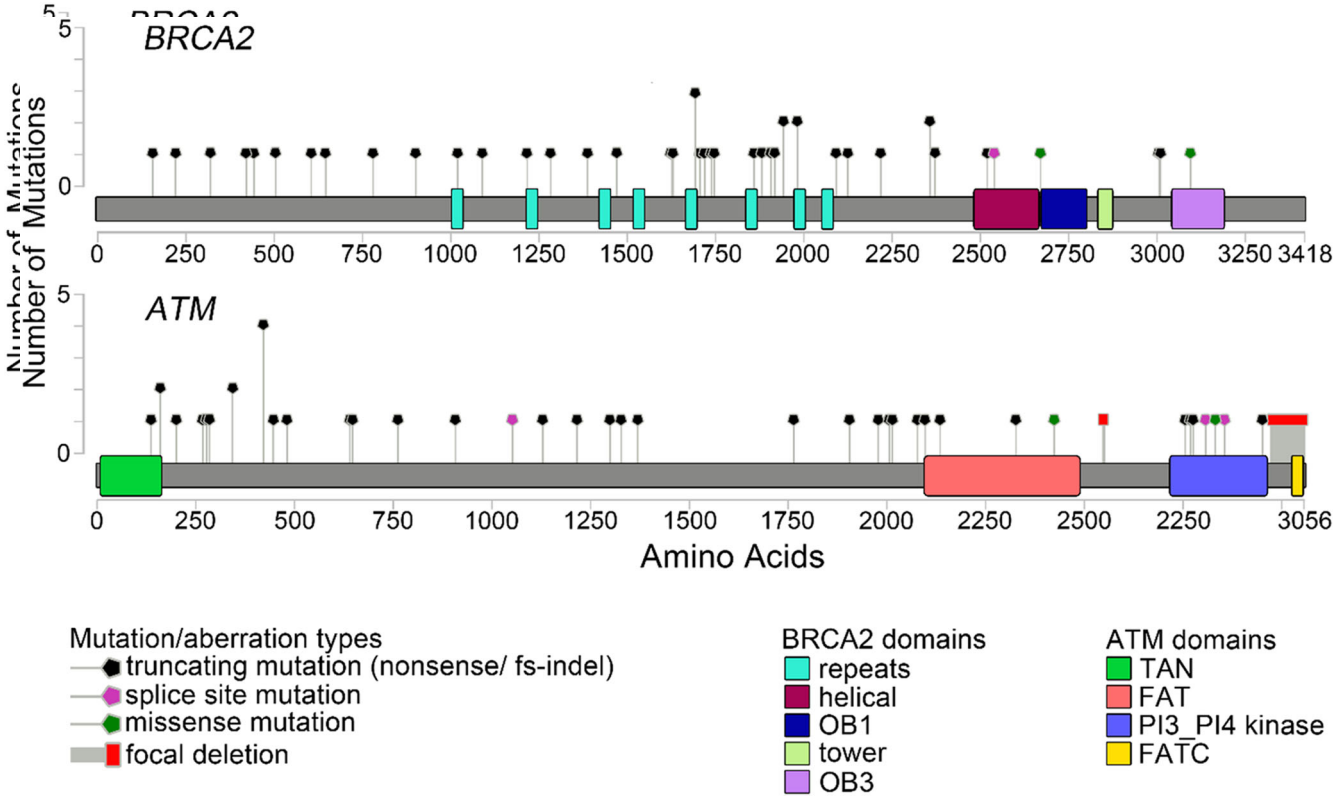

FIGURE 1 Distribution of *ATM* and *BRCA2* mutations [Color figure can be viewed at wileyonlinelibrary.com]

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.

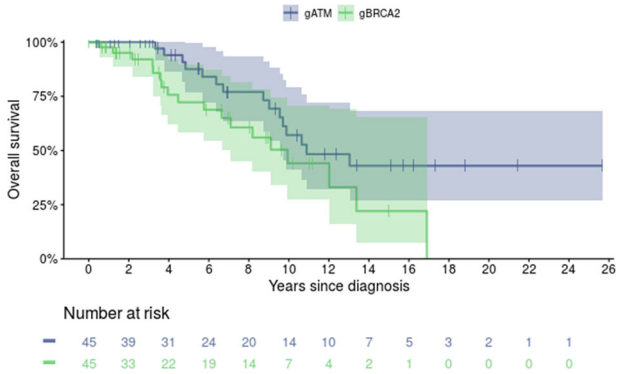

FIGURE 2 Overall survival [Color figure can be viewed at wileyonlinelibrary.com]

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.

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CONFLICT OF INTERESTS

Catherine H. Marshall: Consulting from Dendreon, Bayer, McGraw-Hill Publishing Company. Travel from Dava Oncology.

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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.

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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.

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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

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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Appendix 3

Curricula vitae:

Heather H. Cheng - PI

Evan Y. Yu - co-investigator

Michael T. Schweizer - co-investigator

UNIVERSITY OF WASHINGTON
SCHOOL OF MEDICINE

September 24, 2021

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 Employment: n/a

7. Honors/Awards:

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
2010 University of Washington: Honor Your Physician Award (patient-nominated)
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 11/03/2022
DEA #FC2472328 expires 08/31/2022

10. Professional Organizations:

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

11. Teaching Responsibilities:

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. Internal Medicine Residents, Graduate & Medical Students (*primary mentor)

2017	Paul Katangole, MD, MS, (Uganda Cancer Institute), mentor for NCI Fogarty International Center Fellow Candidate
2018-2019	***Darren Pouv,** University of Washington School of Medicine: MS1, primary research mentor, Independent Investigative Inquiry
2020	Emiko M. Oshima, University of Washington School of Medicine: MPH candidate, research mentoring committee member

B. Subspecialty Fellows (*primary mentor)

2014-2015	Faculty advisor for UW/FHCRC Heme/Onc Fellows' Solid Tumor Conference, biweekly
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 Hematology/Oncology fellow, primary research mentor, current position: **Assistant Professor at Oregon Health Sciences University**
2019-present	**Heme/Onc Fellowship Faculty Champion for Outpatient Genitourinary Oncology Block**
2019-present	Risa Wong, MD, University of Washington/Fred Hutch Hematology/Oncology fellow, research co-mentor, planned position: Assistant Professor at University of Pittsburg
2020-2021	Laura Graham, MD, University of Washington/Fred Hutch Hematology/Oncology fellow, research project co-mentor, current position: Assistant Professor at University of Colorado

Invited Local/Regional Talks:

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. 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.

7. 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

8. 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

9. 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

10. 05/07/2015 *Prostate Cancer: Progress Made and Research in Progress.* Research Matters Series, Seattle Cancer Care Alliance, Seattle, WA

11. 03/24/2016 *Leveraging DNA Repair Defects for Treatment of Prostate Cancer.* PPCR SPORE Seminar Series, Fred Hutchinson Cancer Research Center, Seattle, WA

12. 06/29/2016 *Emerging Therapies in Cancer: Cancer Genetics.* Seattle Cancer Care Alliance CME lecture for Skagit Valley Hospital, Mount Vernon, WA

13. 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

14. 10/27/2016 *Prostate Cancer Foundation Women's Networking Forum*. Junior Investigator Panelist at the 2016 Prostate Cancer Foundation Retreat, Carlsbad, CA

15. 11/17/2016 *Prostate Cancer Genetics: Leveraging Family Traits for Early Detection***.** Fred Hutchinson Cancer Research Center Innovators Network. Seattle, WA

16. 12/23/2016 *Testicular Cancer/Germ Cell Tumors*. UW/Fred Hutch Hematology/Oncology Fellows Lecture Series, Seattle, WA.

17. 03/18/2017 *Inherited Risk and Prostate Cancer Behavior.* Prostate Cancer Symposium, Institute for Prostate Cancer Research; Fred Hutchinson Cancer Research Center, Seattle, WA

18. 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

19. 05/24/2017 *Prostate Cancer Genetics.* UsTOO Greater Seattle Area Prostate Cancer Patient Support Group; Greenwood Community Center, Seattle, WA.

20. 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

21. 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

22. 11/06/2017 *Genetics and Genomics.* CCSG Prostate Program Cancer Retreat, Fred Hutchinson Cancer Research Center, Seattle, WA

23. 01/19/2018 *Testicular Cancer/Germ Cell Tumors*. UW/Fred Hutch Hematology/Oncology Fellows Lecture Series, Seattle, WA.

24. 01/26/2018 *Expanding Clinical and Research Horizons in Prostate Cancer Genetics.* UW Medical Genetics Division Grand Rounds, Seattle, WA

25. 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

26. 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

27. 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

28. 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

29. 05/07/2018 *Prostate Cancer: Screening, Treatment and Genetics.* UW Internal Medicine Residents Report, University of Washington Medical Center, Seattle, WA

30. 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

31. 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

32. 07/17/2018 *Molecular Predictors of Prostate Cancer Progression and Mortality.* PNW SPORE Symposium, Fred Hutch Cancer Research Center, Seattle, WA

33. 08/09/2018 *Prostate Cancer Genetics and the GENTleMEN Study*. Overbaugh Lab 30th Year Symposium Retreat, Islandwood, Bainbridge Island, WA

34. 10/05/2018 *Testicular Cancer/Germ Cell Tumors*. UW/Fred Hutch Hematology/Oncology Fellows Lecture Series, Seattle, WA.

35. 10/12/2018 *Prostate Cancer.* Transitions in Oncology Care: Pearls for the Primary Care Provider Conference, Talaris Conference Center, Seattle, WA.

36. 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

37. 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

38. 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

39. 09/06/2019 *Updates in Prostate Cancer Genetics.* Seattle Cancer Care Alliance Community Site Dinner Clinical Research Partnership Series; Seattle, WA

40. 01/09/2020 *From Cat Viruses to Men's Prostates: An Ongoing Research Journey.* UW Medical Scientist Training Program Monthly Research Meeting; Seattle, WA.

41. 01/24/2020 *Mutational Testing for Solid Tumors.* UW/Fred Hutch Hematology and Oncology Fellowship Solid Tumor Conference; Seattle, WA.

42. 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

43. 05/27/2020: *Prostate Cancer Genetics through a Medical Oncologist's Lens.* University of Washington, Radiation Oncology Grand Rounds, Seattle, WA. [invited Grand Rounds]

44. 07/15/2020: *Olaparib for Metastatic Castration Resistant Prostate Cancer.* Clinical Research Division Journal Watch; Fred Hutch Cancer Research Center, Seattle, WA

45. 07/22/2020: *Prostate Cancer Genetics.* Medscape CME Webinar; Seattle Cancer Care Alliance, Seattle WA

46. 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

47. 02/22/2021: *Prostate Cancer Genetics and Risk.* Seattle Cancer Care Alliance Board Enrichment Series; Seattle Cancer Care Alliance, Seattle WA

48. 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

49. 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

50. 08/25/2021: *Role of Genes in Prostate Cancer and the PROMISE Study.* USToo Support Group Meeting, Seattle, WA

12. Editorial Responsibilities:

Ad Hoc Reviewer for:

British Journal of Cancer
Cancer
Clinical Cancer Research
Clinical Genitourinary Cancer
European Urology
JAMA Oncology
Journal of Clinical Oncology
Journal of Clinical Oncology Precision Oncology
Journal of Oncology Practice
Precision Oncology
Oncotarget

13. 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-	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

14. 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 Hutch/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
2020-present	**Associate Program Director, University of Washington/Fred Hutch Medical Scientist Training Program**
2021	Fred Hutch/UW Cancer Consortium Pilot Award Review Committee
2020-2021	SCCA Genitourinary Medical Oncology Community Research Working Group lead

15. Research Funding

Current Research Support

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: Prostate Cancer Outcomes: An International Registry to Improve Outcomes in Men with Advanced Prostate Cancer (IRONMAN)
Effort: 0.30 calendar
Supporting Agency: Movember (via PCCTC, LLC)
Performance Period: 08/18/17 – 07/31/22
Level of Funding:
Project 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.

Title: PROSTATE CANCER CLINICAL TRIALS CONSORTIUM, W81XWH-17-2-0043 (Cheng)
Effort: 1.80 calendar
Supporting Agency: DOD

Performance Period: 09/30/2017 to 09/29/2021
Level of Funding:
Project Goals: The Department of Defense provides funding for infrastructure to support participation as a clinical site in the Prostate Cancer Clinical Trials Consortium

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: 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, hharbach@fredhutch.org, (206) 667-7245
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: 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
Effort: 0.60 calendar
Supporting Agency: Clovis Oncology, Inc
Performance Period: 07/26/2018 to 08/30/2021
Level of Funding:
Project Goals: The major goal of this trial is to determine radiographic progression free survival with 4 cycles of docetaxel with carboplatin followed by maintenance rucaparib in the treatment of patients with metastatic castration resistant prostate cancer with homologous recombination DNA repair deficiency.

Title: Targeting the Subtype of Metastatic Prostate Cancer Deficient in DNA Repair Capacity Instability Using Targeted Molecular Counting Methods
Effort: 0.60 calendar
Supporting Agency: US Department of Defense (DOD)
Performance Period: 08/01/2018 to 07/31/2021
Level of Funding:
Specific Aims: 1) Determine if germ-line and somatic aberrations in homologous recombination DNA re-pair pathways associate with responses to FDA-approved therapeutics in men with mCRPC. 2) Develop minimally-invasive biomarkers capable of distinguishing patients for therapeutics targeting homologous recombination DNA repair pathways and ascertaining resistance mechanisms. 3) Identify rational drug combinations that exploit DNA repair vulnerabilities to eradicate prostate cancers with homologous recombination repair deficiency.

Title: Clinical qualification of DNA repair defects as biomarkers in metastatic prostate cancer using integrated genomics and tissue-based functional assays
Effort: 0.24 calendar
Supporting Agency: US Department of Defense (DOD)
Performance Period: 08/01/18 to 07/31/21

Level of Funding:
Project 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.

Title: Pacific Northwest (PNW) Prostate Cancer Sponsored Program of Research Excellence (SPORE) Project 1: Molecular Predictors of Prostate Cancer Progression and Mortality
Effort: 1.20 calendar
Supporting Agency: NIH/NCI
Performance Period: 09/01/18 to 08/31/23
Level of Funding: (subaward Y2)
Specific Aims: 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.

Title: CCITLA: Cancer Clinical Investigator Team Leadership Award
Effort: 1.51 calendar
Supporting Agency: NIH/NCI
Performance Period: 03/04/2020 to 02/28/2022
Level of Funding:
Project Goals: The major goal of this award is to develop access to clinical trials for patients using media and expand genetic care using new methods of delivery such as telehealth and molecular tumor boards, disseminating research opportunities to cancer center catchment and region.

Title: ACT PROMISE (Cheng)
Effort: 1.51 calendar
Supporting Agency: DOD PROSTATE CANCER CLINICAL TRIALS CONSORTIUM
Performance Period: 06/19/2020 to 06/30/2022
Level of Funding:
Project 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.

Title: Technology-Enhanced Acceleration of Germline Evaluation for Therapy - The TARGET Study
Effort: 0.6 calendar
Supporting Agency: Prostate Cancer Foundation
Performance Period: 08/06/20 – 12/31/21
Level of Funding:
Specific Aims: The 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.

Title: Enhanced Genetic Awareness and Genetic Evaluation for Men Through Technology - The ENGAGEMENT Study
Effort: 0.60 calendar
Supporting Agency: DOD W81XWH2010310
Contracting/Grants Officer: Jennifer Shankle, jennifer.e.shankle.civ@mail.mil
Performance Period: 09/30/2020-09/29/2023
Level of Funding: (subaward)

Specific Aims: 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.

Pending Research Support

Title: 67652000PCR3002
Effort: TBD
Supporting Agency: Janssen Research & Development, LLC
Contracting/Grants Officer: Sean Murphy: smurph41@its.jnj.com
Performance Period: TBD
Level of Funding: TBD
Project 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.
Overlap: None

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.

16. Bibliography:

Scopus Index (10/11/2021)
h-index: 22
Cumulative citations:

Google Scholar (10/11/2021)
h-index: 24
Cumulative citations:

a) Publications in Refereed Journals

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Profiling Identifies a Subset of Metastatic Prostate Cancer Patients with Evidence of Cancer-Associated Hypoxia*,* PLoS ONE, 2013 Jul 30;8(7). [**original work**]

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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]**

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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]**

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3. **Cheng, H.H.,** Yi, H.S., Tewari M., Pritchard, C.C. Candidate Circulating MicroRNA Cancer Biomarkers Are Altered by Blood Sample Processing. American Society of Clinical Oncology 2012 Markers in Cancer, Abstract #8, Poster discussion session. **(Recipient of Merit Award)**

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80. 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]

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83. 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]

84. 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]

85. **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]

86. 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]

87. 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]

88. 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]

89. 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]

90. 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]

91. Giri, V.N., Gross, L., **Cheng, H.H.,** Russo, J., Paller, C., Johnson, J., Weg, E., 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). [Abstract]

92. 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]

17. National/International Invitational 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]

CURRICULUM VITAE

EVAN YA-WEN YU, MD
Phone: 206-606-7595 Fax:
206-606-2042 Email:
evanyu@uw.edu

PERSONAL DATA

Place of birth:
Citizenship:
Date of Birth:
Languages:

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-present

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-present

Medical Director
Clinical Research Support
Fred Hutchinson Cancer Consortium, Seattle, WA 2018-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
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

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 2021-present
Fred Hutchinson Cancer Research Consortium
Cancer Center Director's Task Force for DEI in Clinical Investigations 2021-present
Fred Hutchinson Cancer Research Consortium

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
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 Urology resident at University of Wisconsin 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 medical student at University of Washington 2019-present
Lorin Ferris – Current medical student at University of Washington 2019-present
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 – Current hematology/oncology fellow	2019-present
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 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 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 Prostate Cancer Translational Grant Study Section	2005
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 Genitourinary Cancer (Prostate) Oral Abstract Session	2010
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 Genitourinary Cancer (Non-Prostate) Oral Abstract Session	2011
Advanced Prostate Cancer Chair (covering), SWOG Fall 2011 Group Meeting Genitourinary Committee	2011

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

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

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 - 09/29/22 (3 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

5. 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
Role: Trial) 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: Cancer Immunotherapy Trials
Source: Network Site principal investigator for
Role: lead site 02/04/15 – 02/03/18
Dates:

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 – 04/14/22

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 – 09/30/22

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 investigator
   Dates: 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 – 02/06/23

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 – 09/30/22

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 cancer.
   Grant 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. 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

2. 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 – 12/31/22

3. 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

4. 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

5. 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

6. 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

7. 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

8. 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

9. 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

10. 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
    Dates: investigator 06/03/20 – 05/31/24

11. 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

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,
   Role: Inc. Site principal
   Dates: investigator 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
Dates: investigator 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 stuydy 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

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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.

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ABSTRACTS (LAST 5 YEARS)

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183. 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.

184. 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.

185. 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.

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87. 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.

88. 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.

89. 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.**

90. 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.

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Poster presentation at Virtual Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2021.

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94. 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.

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99. 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.**

100. 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.

101. 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.

102. 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.

103. 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.

104. 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.

105. 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.

106. 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.

107. 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.

108. 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.

109. 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.

110. 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.

111. 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.

112. 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.

113. 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.

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.

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.

May 13, 2021

Michael Schweizer, MD

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 Research Center*, Seattle, WA
2019 – Present	Associate Professor, Clinical Research Division, *Fred Hutchinson Cancer Research 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, *Seattle Cancer Care Alliance*, Seattle, WA

6. Honors:

2015	Department of Defense Physician Research Training Award
2015	Prostate Cancer Foundation Young Investigator Award
2014 – present	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 – present	American Association for Cancer Research, Member ID: 274966
2014 – Present	Southwest Oncology Group

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 – present	Mentor to Laura Graham MD, Heme-Onc Fellow UW/FHCRC
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

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, Genitourinary Oncology Advanced Disease Meeting

2017 – present Leader, Seattle Cancer Care Alliance, Prostate Cancer Clinical Pathway Team

14. Research Support

Ongoing Research Support:

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

Industry Sponsored Trial Schweizer (PI) 10/14/16 – 06/30/21
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

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

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.
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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

Recently Completed Research:

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

P30 CA015704 Gilliland (PI) 01/01/16 – 12/31/19
Cancer Center Support Grant: New Investigator Support
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 use next generation sequencing to determine the prevalence of genomic hypermutation within the general population of prostate cancer patients and determine if mismatch repair deficiency underlies this phenotype.
Role: Project PI

Industry Sponsored Research Lee (PI) 05/01/18 – 04/30/19
Therapeutic Targeting of Castration-Resistant Prostate Cancer with the CEACAM5 Antibody-drug Conjugate (ADC) IMMU-130 and the Trop2 ADC IMMU-132
The major goal of this study is to profile the expression of the tumor antigens CEACAM5 and Trop2 in metastatic prostate cancers and to tests antibody drug conjugates targeting these antigens in preclinical models of androgen receptor-null prostate cancer.
Role: Co-Investigator

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49. **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]

50. **Schweizer, M.T.** & Yu, E.Y. Persistent androgen receptor addiction in castration-resistant prostate cancer. Journal of hematology & oncology 8, 128 (2015). [review]

51. **Schweizer, M.T.** & Antonarakis, E.S. Liquid biopsy: Clues on prostate cancer drug resistance. Science translational medicine 7, 312fs345 (2015). [review]

52. 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]

53. ***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]

54. 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]

55. 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]

56. 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]

57. **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]

58. **Schweizer, M.T.** & Drake, C.G. Immunotherapy for prostate cancer: recent developments and future challenges. Cancer metastasis reviews 33, 641-655 (2014). [review]

59. **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]

60. **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]

61. **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]

62. **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]

63. **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]

64. **Schweizer, M.T.** & Antonarakis, E.S. Abiraterone acetate: a hat trick of clinical benefits. The Lancet. Oncology 13, 1173-1174 (2012). [review]

65. **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]

66. **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. 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.

2. **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

3. **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.

4. **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.

5. **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.

6. **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.

7. **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.

8. **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.

9. **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.

10. **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:

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. 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).
2. 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).
3. 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).