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TITLE: Prostpective-Retrospective Analysis of PTEN Immunohistochemistry Assay for Prediction of Outcomes in Recurrent and Metastatic Prostate Cancer

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CONTRACTING ORGANIZATION: Johns Hopkins University
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Johns Hopkins University
Baltimore, MD, 21231

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Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

As part of the CDMRP-funded Precision Medicine Biomarker Validating Center, we have developed a robust, highly analytically validated and cost-effective immunohistochemistry (IHC)-based assay to interrogate PTEN loss in prostate cancer. Our PTEN assay is prognostic in multiple cohorts of surgically-treated prostate cancer patients; now, we propose to leverage this body of previous validation studies to test the hypothesis that PTEN loss in primary prostate cancer predicts for a less robust response to hormonal therapies, in the context of two recent, practice-changing Phase III clinical trials for which we have CTEP approval to access specimens. Here, we report on progress to date. We have obtained tissue microarrays containing tissues from 306 patients for RTOG96-01 and immunostained them for PTEN and ERG. In initial analyses, patients with intact PTEN have a 50% decrease in cumulative incidence of metastasis with combined radiation therapy and anti-androgen therapy compared to radiation therapy alone, while patients with PTEN loss do not see the benefit of additional anti-androgen therapy.

15. SUBJECT TERMS
Prostate cancer, PTEN, ERG, immunohistochemistry, survival, radiation therapy, anti-androgen therapy

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	12	19b. TELEPHONE NUMBER *(include area code)*

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1. **INTRODUCTION:**

With the completion of The Cancer Genome Atlas (TCGA) and Stand Up to Cancer (SU2C) sequencing projects for primary and metastatic prostate tumors, the genomic landscape of prostate cancer has largely been elucidated. Yet currently, none of the findings in these studies have improved patient outcomes in the disease, in large part because of the challenges associated with validating prognostic and predictive genomic biomarkers. Among the genomic changes cataloged, PTEN is the earliest and most commonly lost tumor suppressor in primary prostate cancers and its loss portends a poor prognosis and is associated with the development of castrate resistant disease in pre-clinical models. As part of the CDMRP-funded Precision Medicine Biomarker Validating Center, we have developed a robust, highly analytically validated and cost-effective immunohistochemistry (IHC)-based assay to interrogate PTEN loss in prostate cancer. Based on this work, these assays are currently performed in the Johns Hopkins CLIA/CAP-accredited Immunopathology Laboratory.

Hypothesis/Objective: Our PTEN assay is prognostic in multiple cohorts of surgically-treated prostate cancer patients; here, we will leverage this body of previous validation studies to test the hypothesis that **PTEN loss in primary prostate cancer predicts for a less robust response to hormonal therapies**, in the context of two recent Phase III clinical trials for which we have CTEP approval to access specimens.

Here, **we will test the hypothesis generated by preclinical models that PTEN loss predicts for a less robust response to AR-targeted and/or and androgen deprivation therapies**. More specifically, in the context of ECOG 3805, we will examine whether patients with PTEN-deficient metastatic prostate tumors derive additional benefit from docetaxel chemotherapy deployed with androgen deprivation therapy. In the context of RTOG 96-01, we will test whether the addition of AR-targeted therapy to radiation therapy is less beneficial for patients with patients with PTEN-deficient recurrent non-metastatic prostate tumors. In each study, we will further assess whether ERG status modulates the relationship of PTEN to clinical outcomes.

2. **KEYWORDS:** Prostate cancer, PTEN, ERG, immunohistochemistry, survival, radiation therapy, anti-androgen therapy

3. **ACCOMPLISHMENTS:**

What were the major goals of the project?

a. **Specific Aim 1: Test whether PTEN status modifies benefit associated with treatment in ECOG 3805, a phase III trial that demonstrated a benefit for docetaxel chemotherapy at the time of starting androgen deprivation therapy (AAT) for men with high volume metastatic disease.**
    1. **Determine PTEN/ERG status of ~300 tumors from trial (~150 in each arm)**
        a. Obtain HRPO Approval for study (Hopkins IRB approval is in place already)
        b. Obtain tissue slides from ECOG in batches of 30
        c. Immunostain and blindly score for PTEN/ERG status

2. **Integrate PTEN/ERG status with de-identified clinical-pathologic data for study patients received from ECOG.** The primary objective will be to assess whether the relative benefit of docetaxel+AAT (androgen deprivation therapy) differs in patients with PTEN loss compared to PTEN intact. Secondary objectives will be to examine the association of PTEN status with outcome, stratified by treatment arm, ERG status, and/or low/high tumor volume.

b. **Specific Aim 2: Test whether PTEN status modifies the benefit associated with treatment in RTOG 96-01, a phase III trial that demonstrated a benefit for AR-targeted therapy with bicalutamide at the time of radiation therapy for non-metastatic PSA recurrence after radical prostatectomy.**
   1. **Construct Tissue microarray and determine PTEN/ERG status of ~550 tumors from trial**
      a. Obtain HRPO Approval for study (Hopkins IRB approval is in place already)
      b. Generate tissue microarrays (TMAs) from 335 radical prostatectomy specimens in the study; receive ~212 slides of cases with slides available from NRG
      c. Immunostain TMAs and tissue slides and blindly score for PTEN/ERG status
   2. **Integrate PTEN/ERG status with de-identified clinical-pathologic data for study patients received from NRG.** The primary objective will be to assess PTEN status by immunohistochemistry (IHC) and assess whether PTEN status modifies the association of treatment (radiation therapy vs. radiation therapy+anti-androgen therapy) with metastasis free survival in patients treated with salvage radiation after biochemical recurrence. Secondary objectives will include similar evaluations of combined PTEN-ERG status, and whether PTEN or PTEN-ERG status are prognostic in these patients, independent of treatment. PTEN/ERG status may also be correlated with next generation sequencing data generated by the Maher-Feng-Tomlins study of the same specimens which is already approved

What was accomplished under these goals?

1) Major activities during this reporting period include progress on studies involving RTOG96-01. In the previous reporting period, tissue microarrays containing 320 radical prostatectomies from patients in the trial were created by the RTOG tissue biorepository team. Unstained slides from these tissues were sent to Johns Hopkins and have been stained for PTEN and ERG and scanned images segmented and made available on our internal TMAJ viewer for scoring. Scoring is now completed for both of these biomarkers and the initial analysis of the data from this cohort is described below. An additional 194 cases with unstained slides available were also shipped to Johns Hopkins and are currently undergoing immunostaining. Analyses from this additional subset will be reported in the next period.

2) Specific objectives during this reporting period were to immunostain, score and analyze PTEN and ERG status of tumors available on tissue microarrays in the RTOG 96-01 trial.

3) Significant results or key outcomes: Limited human data and pre-clinical mouse models have shown that prostate tumors with PTEN loss have lower androgen receptor (AR) levels and AR signaling output compared to those with intact PTEN. We tested whether PTEN status modifies

the benefit associated with treatment in RTOG 96-01, a phase III trial that demonstrated a benefit for anti-androgen therapy (AAT) with bicalutamide at the time of radiation therapy (RT) for non-metastatic PSA recurrence after radical prostatectomy. Using a genetically validated assay, we performed PTEN/ERG immunohistochemistry on primary prostate cancer (PCa) from 146 patients with interpretable staining treated with RT/AAT vs. 160 patients with interpretable staining treated with RT alone; these were subsets with tissue available on tissue microarray (TMA) from the total 760 enrolled. The primary focus of the analysis was to determine whether the response to RT/AAT for metastasis differed for those with PTEN loss vs. intact. The analysis used Cox proportional hazards regression to evaluate metastasis-free survival (MFS), accounting for competing risk due to death from causes other than prostate cancer.

Altogether, 97% (304/312) of cases had interpretable staining for PTEN and 99% (309/312) had interpretable results for ERG. Overall, 32.9% (97/304) of cases had PTEN loss and 50.5% (156/309) of cases were positive for ERG. Table 1 compares the distribution of demographic, clinical and biomarker values for RT/AAT vs. RT. There were no significant differences, indicating that the covariate balance achieved by the randomization of all patients in the trial was maintained in the subset analyzed here. The cumulative incidence of metastasis at 12 years was 18.0% for RT/AAT patients vs. 24.5% for RT patients. This is similar to the 12 year cumulative incidence of metastasis observed for the entire trial of 14.5% vs. 23.0% (1). Prevalence of PTEN loss (heterogeneous or homogeneous) in RT/AAT vs. RT patients was 29.6% vs. 34.0%, p=0.414.

For multivariable analyses there were 283 (92.5%) patients (135 RT/AAT, 148 RT) with non-missing values for treatment group, PTEN, metastasis outcome and survival time, and clinical variables. A Cox proportional hazards model (PHM) evaluated race (white vs. other), Gleason grade (GG1, GG2, GG3, GG4, GG5), clinical stage (cT3 vs. cT2), and margin status to identify potential confounding factors to be controlled in the analyses. The only variable that was statistically significant was GG5 vs. GG1-GG4, hazard ratio (HR) =6.2 (95% CI: 2.7, 13.9), p<0.0001. Table 2 shows results of models with treatment group alone; treatment and GG5; PTEN alone; treatment group, GG5, and PTEN; and treatment group, PTEN, interaction of PTEN and treatment, and GG5.

For RT/AAT vs RT, HR=0.63 (95% CI: 0.38, 1.04). This is similar to the hazard ratio for metastasis in analysis of the entire RTOG9601 trial, HR=0.63 (95% CI: 0.46, 0.87). This suggests that the subset analyzed here is representative of the patients in the trial as a whole. Figures 1-3 show cumulative incidence of metastasis, prostate cancer specific death, and Kaplan-Meier for overall survival, respectively, for RT/AAT (red line) and RT (blue line).

PTEN loss was not statistically significant, HR=1.20 (95% CI: 0.72, 1.98), and there was little difference in the effect of PTEN heterogeneous or homogenous loss, HR=1.10 (95% CI: 0.57, 2.12), and HR=1.30 (95% CI: 0.69, 2.44). When included in a model with treatment group and GG5, PTEN loss remained not significant, HR=1.07 (95% CI: 0.63, 1.82). There was a strong suggestion of an interaction between treatment group and PTEN, i.e. for RT/AAT vs RT among patients with PTEN intact HR=0.52 (95% CI: 0.27, 1.00), compared to RT/AAT vs RT among patients with PTEN loss, HR=1.04 (95% CI: 0.45, 2.39). In other words, among patients with PTEN intact, the risk of metastasis was nearly 50% lower among patients with RT/AAT

compared to RT, but in patients with PTEN loss metastasis was virtually identical in both treatment groups. However, the interaction was not statistically significant, p=0.206.

PTEN loss was not significantly associated with cumulative incidence of prostate cancer specific death, HR=1,38 (95% CI: 0.74, 2.57), p=0.313, or overall survival, HR=0.79 (95% CI: 0.50, 1.23), p=0.29. Figures 4-6 show cumulative incidence of metastasis, prostate cancer specific death, and Kaplan-Meier for overall survival, respectively, for PTEN loss (red line) vs. PTEN intact (blue line).

In sum, in this subset of the RTOG96-01 trial population, PTEN was not significantly associated with cumulative incidence of metastasis, prostate cancer death, or overall-survival. RT/AAT had a similar absolute reduction in cumulative incidence of metastasis as observed in the trial as a whole, HR=0.63, but was not statistically significant, p=0.073. There was a strong suggestion of an interaction between PTEN and RT/AAT, i.e. among patients with PTEN intact RT/AAT reduced cumulative incidence of metastasis by nearly 50%, HR=0.52, while among patients with PTEN loss there was no difference between RT/AAT and RT, HR=1.04 (Figures 7 and 8). The interaction was not statistically significant, p=0.206. However, tests for interaction typically have low power and examination of an additional ~200 patients with unstained slides (not present on tissue microarrays) is ongoing.

Table 1. Comparison of bicalutamide and placebo patients.

Variable	Bicalutamide (n=146)	Placebo (n=160)	p-value
Age, yrs; median (IQR)	63.5 (59.0-69.0)	64.0 (61.0-70.0)	0.102
Race, n (%)			
White	131 (89.7)	138 (86.3)	0.648
Black	11 (7.5)	16 (10.0)	
Other	4 (2.7)	6 (3.8)	
Gleason grade, n (%)			
1	49 (34.8)	43 (27.6)	0.242
2	41 (29.1)	57 (36.5)	
3	32 (22.7)	28 (18.0)	
4	12 (8.5)	13 (8.3)	
5	7 (5.0)	15 (9.6)	
Clinical stage, n (%)			
T2	50 (34.3)	52 (32.5)	0.746
T3	96 (65.8)	108 (67.5)	
Positive margins, n (%)			
Yes	110 (75.3)	121 (75.6)	0.954
No	36 (24.7)	39 (24.4)	
Prior hormone therapy, n (%)			
No neoadjuvant	139 (95.2)	149 (93.1)	0.476
Neoadjuvant	7 (4.8)	11 (6.9)	
Salvage hormone therapy, n (%)			

None	107 (73.3)	92 (57.5)	1.00
Hormone therapy	39 (6.7)	67 (41.9)	
Orchiectomy	0 (0)	1 (0.6)	
PTEN, n (%)			
Loss	42 (29.6)	55 (34.0)	0.414
Intact	100 (70.4)	107 (66.1)	
ERG, n (%)			
Negative	67 (45.6)	86 (53.1)	0.187
Positive	80 (54.4)	76 (46.9)	
Outcome, n (%)			
Censored alive w/o mets	90 (61.6)	87 (54.4)	0.242
Metastasis	26 (17.8)	41 (25.6)	
Death other causes w/o mets	30 (20.6)	32 (20.0)	

Table 2. Cox proportional hazards competing risk models of metastasis-free survival

Model	HR (95% CI)*	p-value
Model 1		
Race (white vs. other)	0.77 (0.38, 1.56)	0.470
GG2	1.32 (0.66, 2.64)	0.440
GG3	1.56 (0.73, 3.34)	0.249
GG4	1.07 (0.34, 3.41)	0.909
GG5	6.16 (2.73, 13.93)	<0.0001
Clinical stage (cT3 vs. cT2)	1.33 (0.68, 2.610	0.407
Positive margins	0.60 (0.34, 1.06)	0.080
Model 2		
Treatment (RT/ADT vs RT)	0.63 (0.38, 1.04)	0.073
Model 3		
Treatment (RT/ADT vs RT)	0.67 (0.40, 1.11)	0.122
GG5 vs GG1-GG4	4.63 (2.51, 8.56)	<0.0001
Model 4		
PTEN (loss vs. intact)	1.20 (0.72, 1.98)	0.488
Model 5		
PTEN intact	Ref	
PTEN heterogzygous loss	1.10 (0.57, 2.12)	0.776
PTEN homozygous loss	1.30 (0.69, 2.44)	0.413
Model 6		
Treatment (RT/ADT vs RT)	0.67 (0.40, 1.12)	0.130
GG5 vs GG1-GG4	4.60 (2.46, 8.61)	<0.0001
PTEN loss vs. intact	1.07 (0.63, 1.82)	0.796
Model 7		
PTEN intact:		
Treatment (RT/ADT vs RT)	0.52 (.27, 1.00)	0.206**
PTEN loss:		
Treatment (RT/ADT vs RT)	1.04 (0.45, 2.39)	
GG5 vs GG1-GG4	4.49 (2.40, 8.39	<0.0001

* Abbreviations: HR, hazard ratio; CI, confidence interval; RT, radiotherapy; ADT, bicalutamide

** This p-value is based on the overall effect of the interaction, and reflects the statistical significance of the *difference* in HRs associated with RT/ADT among patients with PTEN intact compared to the RT/ADT effect in patients with PTEN loss.

Figure 1. Cumulative Incidence of metastasis for RT/AAT vs. RT

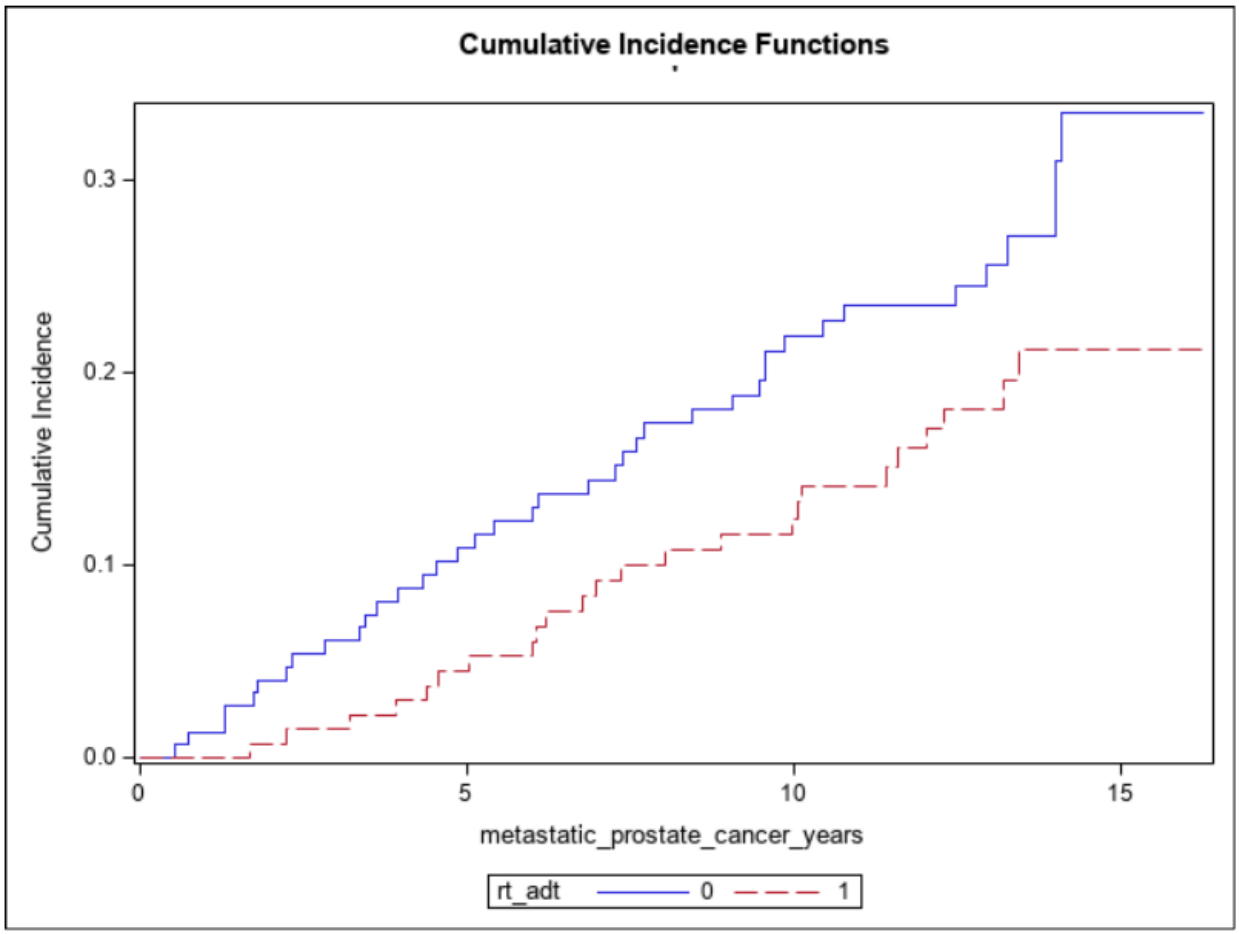


Figure 2. Cumulative Incidence of prostate cancer death for RT/AAT vs. RT

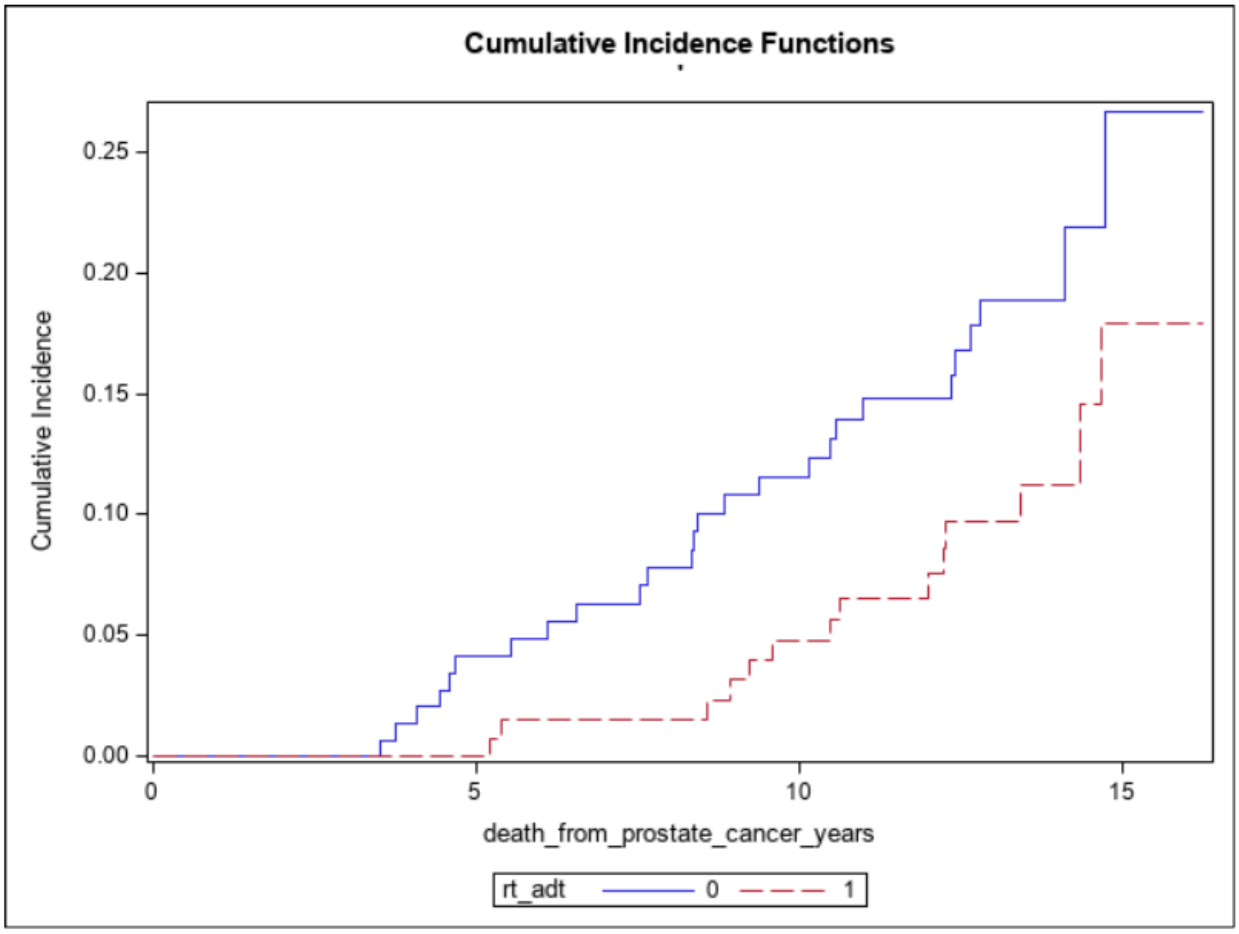


Figure 3. Kaplan-Meier curve for overall survival in RT/AAT vs. RT

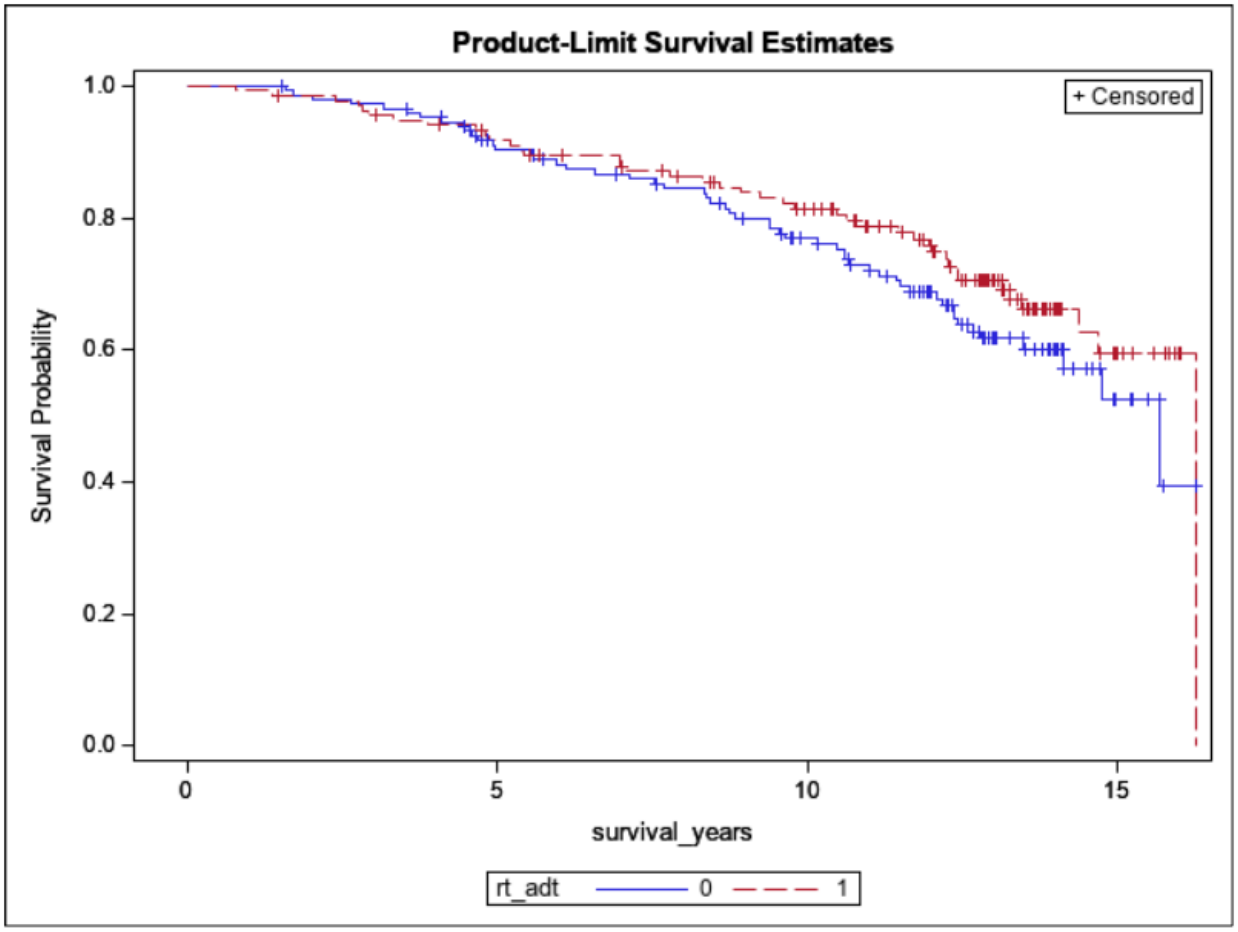


Figure 4. Cumulative Incidence of metastasis for PTEN loss vs. PTEN intact

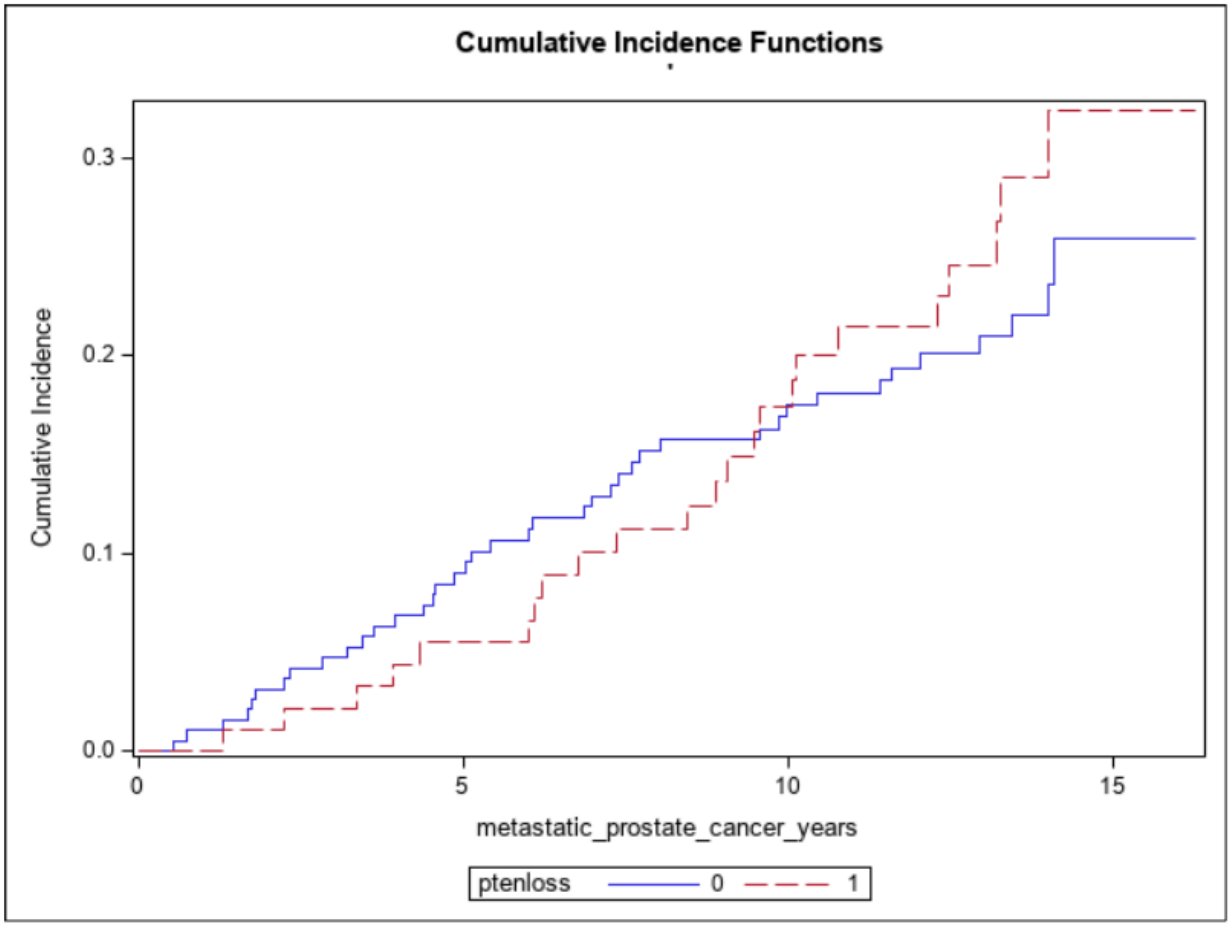


Figure 5. Cumulative Incidence of prostate cancer death for PTEN loss vs. PTEN intact

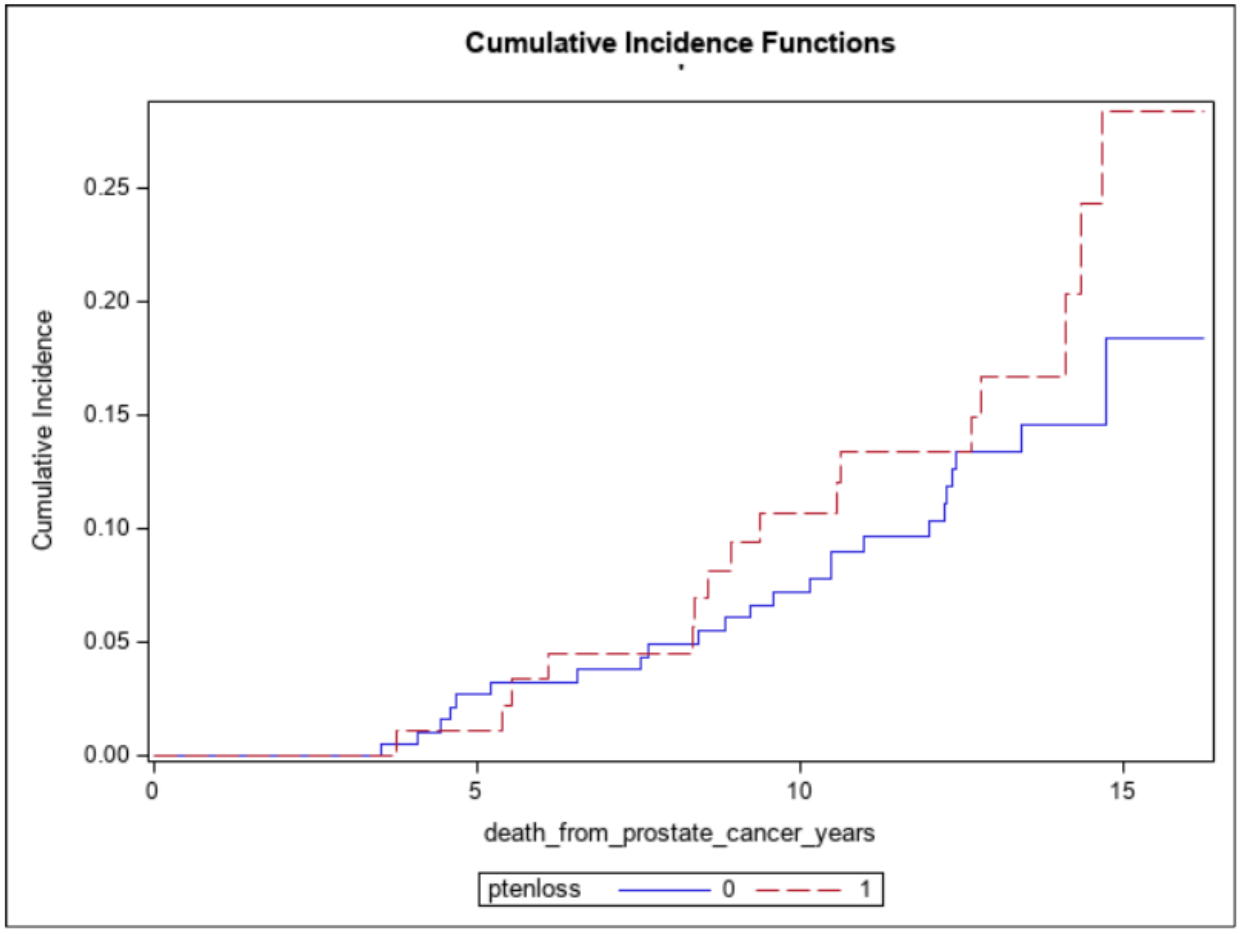


Figure 6. Kaplan-Meier of overall survival for PTEN loss vs. PTEN intact

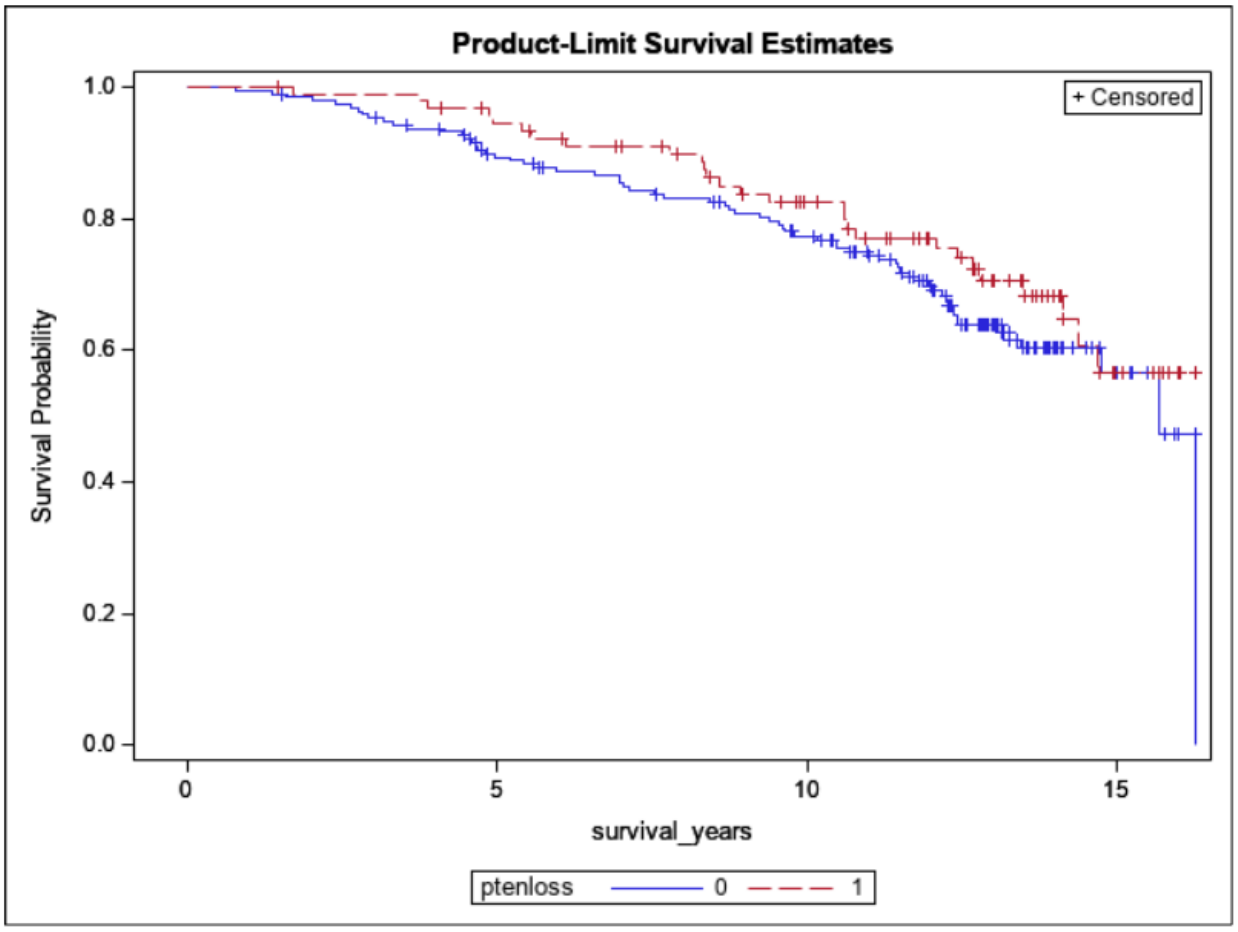


Figure 7. Cumulative incidence of metastasis for patients with PTEN intact

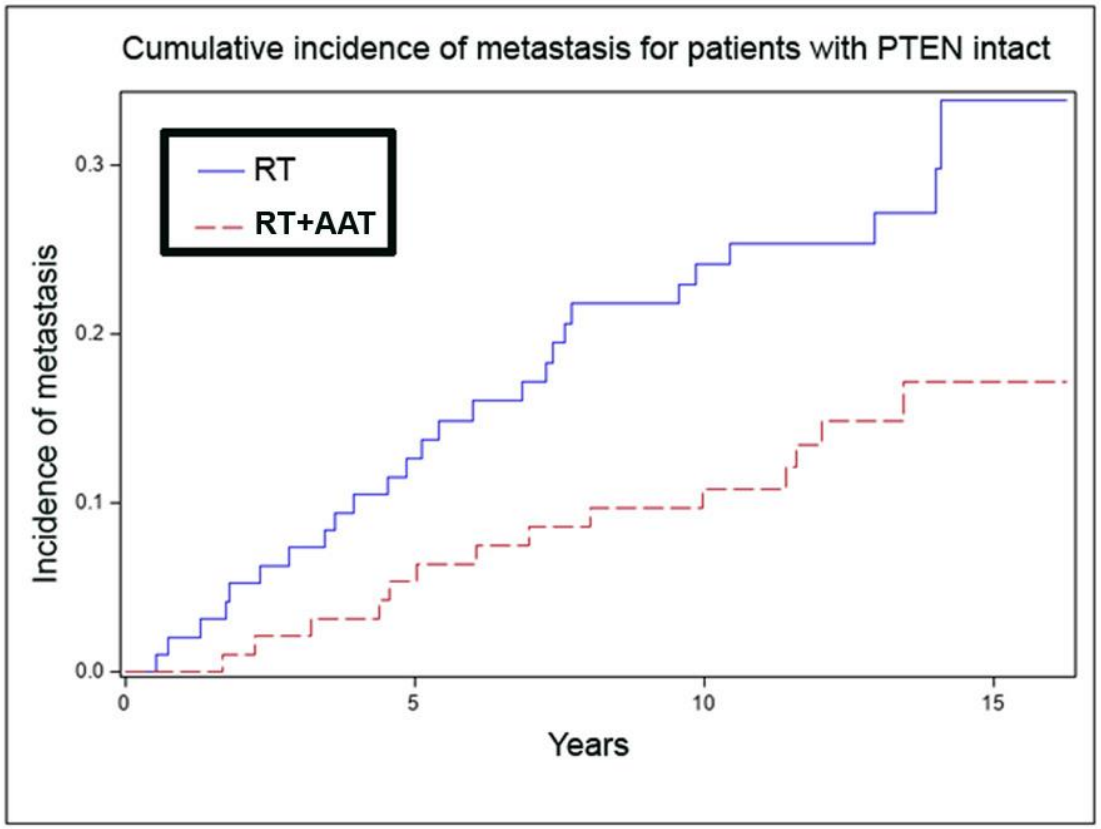
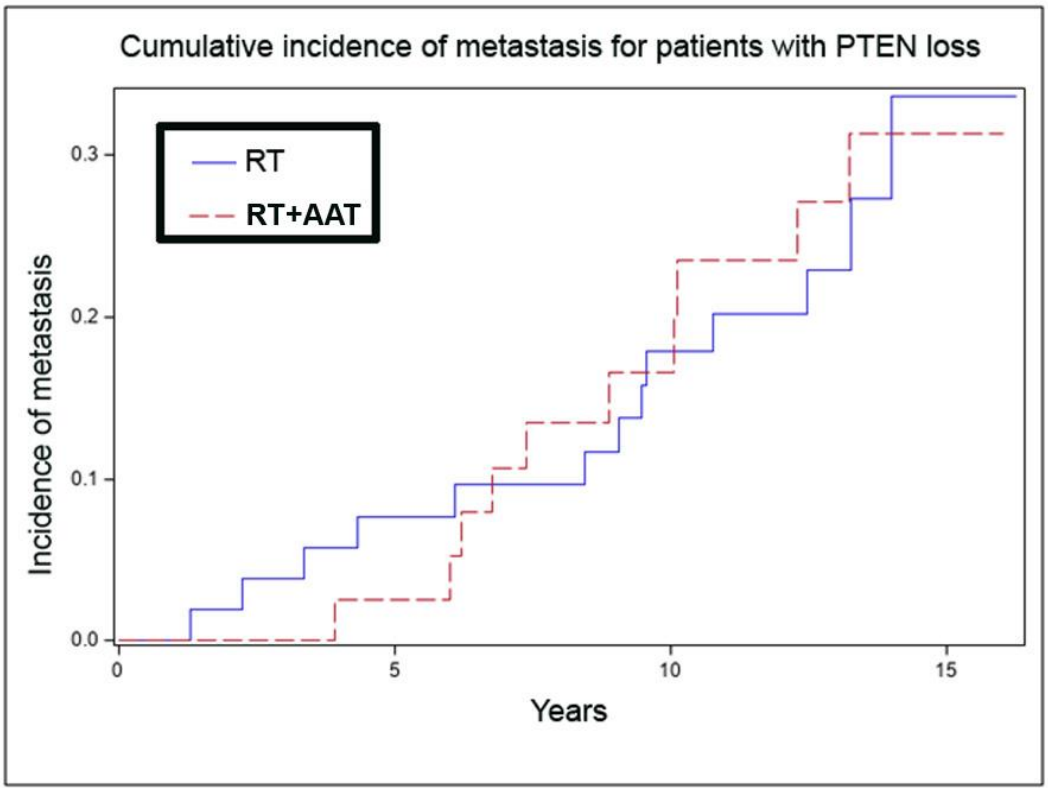


Figure 8. Cumulative incidence of metastasis for patients with PTEN intact



REFERENCES

1. Shipley WU, Seiferheld W, Lukka HR, Major PP, Heney NM, Grignon DJ, et al. Radiation with or without Antiandrogen Therapy in Recurrent Prostate Cancer. The New England journal of medicine. 2017;376(5):417-28.

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

Nothing to report

What do you plan to do during the next reporting period to accomplish the goals?

In the next reporting period, we will focus on performing and analyzing the ERG immunohistochemistry for ECOG3805 and analyzing the ERG for RTOG96-01. In addition, we will examine the interaction between PTEN and ERG with therapy arm in ECOG3805 and RTOG96-01. Finally, we will finish the immunstaining of the ~200 additional cases from RTOG96-01 for PTEN and ERG which is underway currently and add these cases to the analysis.

IMPACT

What was the impact on the development of the principal discipline(s) of the project?

We have successfully determined PTEN status on 306 cases from both arms of the landmark RTOG96-01 trial. We see a trend that patients with PTEN loss may not derive the same benefit from addition of AAT to RT compared to patients with PTEN intact. If replicated in the additional samples (and statistically significant), these results suggest that PTEN may useful to determine which patients should get AAT when undergoing RT for biochemical recurrence after radical prsotatectomy. Given that AAT is associated with significant morbidity, biomarker selection could significantly improve patient case in this setting.

What was the impact on other disciplines?

Nothing to Report

What was the impact on technology transfer?

Nothing to Report

What was the impact on society beyond science and technology?

Nothing to Report

4. CHANGES/PROBLEMS

Changes in approach and reasons for change

Nothing to report

Actual or anticipated problems or delays and actions or plans to resolve them

Nothing to report

Changes that had a significant impact on expenditures

Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to report

Significant changes in use or care of human subjects

Nothing to report

Significant changes in use or care of vertebrate animals.

Not applicable

Significant changes in use of biohazards and/or select agents

Not applicable

5. **PRODUCTS:** *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

Publications, conference papers, and presentations

An abstract describing the RTOG96-01 work was successfully submitted for the USCAP (United States and Canadian Association of Pathology) 2020 meeting and we are awaiting results of review.

Journal publications.

Nothing to report

Books or other non-periodical, one-time publications.

Nothing to report

Other publications, conference papers, and presentations.

Nothing to report

Website(s) or other Internet site(s)

Nothing to report

Technologies or techniques

Nothing to report

Inventions, patent applications, and/or licenses

Nothing to report

Other Products

Database of PTEN/ERG status in ECOG3805 and RTOG 96-01 trial patients. We will make this available to other researcher upon publication via ECOG and NRG.

6. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	*Tamara Lotan*
Project Role:	*PI*
Researcher Identifier (e.g. ORCID ID):	*Tlotan1*
Nearest person month worked:	*1*
Contribution to Project:	*Dr. Lotan supervised IHC data collection and interpretation.*
Funding Support:	*NCI/NIH, CDMRP-PCRP*

Name:	*Sanjana Murali*
Project Role:	*Research technician*
Researcher Identifier (e.g. ORCID ID):	*NA*
Nearest person month worked:	*7*
Contribution to Project:	*Ms. Murali performed IHC data collection and interpretation.*
Funding Support:	*CDMRP-PCRP*
Name:	*Harsimar Kaur*

Project Role:	*Postdoctoral fellow*
Researcher Identifier (e.g. ORCID ID):	*NA*
Nearest person month worked:	*4*
Contribution to Project:	*Dr. Kaur performed IHC data collection and interpretation.*
Funding Support:	*CDMRP-PCRP*

Name:	*Bruce Trock*
Project Role:	*Co-investigator*
Researcher Identifier (e.g. ORCID ID):	*Btrock1*
Nearest person month worked:	*1*
Contribution to Project:	*Dr. Trock performed statistical data analysis*
Funding Support:	*NCI/NIH, CDMRP-PCRP*

Name:	*Angelo De Marzo*
Project Role:	*Co-investigator*
Researcher Identifier (e.g. ORCID ID):	*Ademarz1*
Nearest person month worked:	*1*
Contribution to Project:	*Dr. De marzo assisted with IHC interpretation and data analysis interpretation*
Funding Support:	*NCI/NIH, CDMRP-PCRP*

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Yes, Dr. Lotan added the additional grants listed below:

Award ID: PC181023
Title: Epigenomic Landscape of Primary Prostate Cancer in African-American Men
Effort: 1.20 calendar months (10% effort)
Supporting Agency: DOD PCRP Health Disparity Award
Grants officer: TBD
Address of Funding Agency: 820 Chandler Street, Fort Detrick, MD 21702-5014
Performance Period: 06/01/2019 – 05/31/2022
Level of Funding: $1,516,374
Principal Investigator: Tamara Lotan
Project Goal: To identify epigenomic markers of lethal prostate cancer in African American men.
Specific Aims:
Aim 1: Identify differentially methylated CpG sites associated with genetic racial ancestry, oncologic outcomes, somatic genomic alterations and immune response in a retrospective Johns Hopkins (JHH) cohort of matched primary PCa from 200 AA and 200 WH men at radical prostatectomy Aim 2: Validate epigenomic signatures associated with racial ancestry and adverse oncologic outcomes in AA patients using the Baylor College of Medicine (BCM) retrospective cohort of 300 AA tumors at radical prostatectomy with long term follow-up.
Aim 3: Validate epigenomic signatures associated with pathologic tumor aggression, genetic racial ancestry; somatic genomic alterations and immune microenvironment alterations in AA patients using the RESPOND cohort of 400 prospectively collected AA tumors.
Projects Overlap or Parallel: no scientific or budgetary overlap

Award ID: 109644168
Title: Research on Prostate Cancer in Men of African Ancestry: Defining the Roles of Genetics, Immunity and
Access to Care (RESPOND)
Effort: 1.80 calendar months (15% effort)
Supporting Agency: University of Southern California
Grants Officer: Lillian Rivera
Address of Funding Agency: 2001 Soto Street, SSB-205, Los Angeles, CA 90089-9235
Performance Period: 07/05/2018-06/30/2023
Level of Funding: $3,226,742
Principal Investigator: Chris Haiman (University of Southern California)
Project Goals: The major goal of this project is to assemble a prospective cohort of African-American prostate cancer patients from SEER registries across the country. Dr. Lotan will lead the Pathology Core for this project, processing ~3000 prostate cancer tumor specimens from this cohort.
Projects Overlap or Parallel: no scientific or budgetary overlap.

Award ID: PCF Challenge Award
Title: Dissecting the prostate cancer diaspora
Effort: 0.12 calendar months (1% effort)
Supporting Agency: Prostate Cancer Foundation
Grants Officer: Audrey Gardner
Address of Funding Agency: 1250 Fourth Street, Santa Monica, CA 90401

Performance Period: 02/01/2019-01/31/2021
Level of Funding: $500,000
Principal Investigator: Kenneth Pienta
Project Goal: The primary goal of this project is to determine the rate of CTC production in men with biochemical recurrence and oligometatatic disease in prostate cancer.
Specific Aims: 1. We hypothesize that men in the BCR group will have detectable CTCs if they are in the bone only or LN + bone groups. Only a minority of men with prostate bed or LN only disease will have detectable CTCs. 2. We hypothesize that in men with OM by conventional imaging will have progressed to a systemic disease state and will have detectable CTCs.
Projects Overlap or Parallel: no scientific or budgetary overlap.

Award ID: PC180810
Title: Genetic and genomic determinants of homologous recombination repair deficiency as treatment selection markers for lethal prostate cancer
Effort: 0.60 calendar months (5% effort)
Supporting Agency: Department of Defense, Congressionally Directed Medical Research Programs (CDMRP)
Grants Officer: TBD
Address of Funding Agency: 820 Chandler Street, Fort Detrick, MD 21702
Performance Period: 07/01/2019 – 06/30/2022
Level of Funding: $600,000
Principal Investigator: Jun Luo
Project Goal: The overall goal of this project is to test the hypothesis that mCRPC patients can be categorized into three groups according to HRD status defined by deleterious mutations in HRD genes.
Specific Aims: 1.To ascertain the HRD mutations status, both somatic and germline, in three existing advanced/lethal prostate cancer cohorts enriched for HRD using blood-based assays. 2. To determine the association of HRD status defined by blood-based assays with treatment response to first-line AR-directed therapy (abiraterone/enzalutamide) and taxane chemotherapies in mCRPC patients by comparing treatment outcomes of men in these three groups. 3. To determine the expression correlates of HRD status defined by blood-based assays and further ascertained by tissue-based assays, by performing RNA-Seq in surgical specimens from men with lethal prostate PCa with: 1) germline/somatic HRD; 2) somatic-only HRD; and 3) negative HRD.
Projects Overlap or Parallel: no scientific or budgetary overlap

Award ID: PC180375
Title: Discovery and Functional Analyses of Susceptibility Genes for Lethal Prostate Cancer
Effort: 0.60 calendar months (5% effort)
Supporting Agency: Department of Defense, Congressionally Directed Medical Research Programs (CDMRP)
Grants Officer: TBD
Address of Funding Agency: 1077 Patchel Street, Fort Detrick, MD 21702-5024; 301-619-7782
Performance Period: 07/01/2019 – 06/30/2021

Level of Funding: $306,016
Principal Investigator: William Isaacs
Project Goal: The goal of this project is to ascertain a set of candidate susceptibility genes for aggressive prostate cancer can be used to identify men at risk for aggressive/lethal disease.
Specific Aims: 1. To identify candidate germline susceptibility alleles by analyzing whole-exome sequencing data from 6000 patients of European and African descent. 2. Assess the functional characteristics of our top 45 candidate APCa genes identified in Specific Aim 1.
Projects Overlap or Parallel: no scientific or budgetary overlap

Award ID: R01 CA240343
Title: Stromal senescence in lethal prostate cancer: a novel target for prognosis and therapy
Effort: 0.30 calendar months (2.5% effort)
Supporting Agency: National Institutes of Health
Grants Officer: Leota Hall
Address of Funding Agency: 9000 Rockville Pike, Bethesda, MD 20892
Performance Period: 07/01/2019 – 06/30/2023
Level of Funding: $278,539
Principal Investigator: Elizabeth Platz
Project Goal: Address the overarching hypothesis that the stromal senescence-associated secretory phenotype (SASP) especially one that elicits an inflammatory response (productive SASP). Promotes a lethal prostate cancer phenotype.
Specific Aims:
Projects Overlap or Parallel: no scientific or budgetary overlap

Award: W81-XWH-19-1-0781
Title: mTORC1 Regulates MiTF Expression and Lysosomal Biogenesis
Effort: .24 calendar months (2% effort)
Supporting Agency: Department of the Army
Name of Procuring Contracting/Grants Officer: Jason D. Kuhns
Address of Funding Agency: 820 Chandler Street, Fort Detrick, MD 21702-5014
Performance Period: 08/01/2019 – 07/31/2021
Level of Funding: $163,750
Principal Investigator: Kaushal Asrani
Project Goals: The major goal of this project is to study the regulation of MiT/TFE gene expression and determine whether MiT/TFE over-expression and a concomitant increase in lysosomal biogenesis are key drivers of tumorigenesis following TSC1/2 loss.
Specific Aims: Aim 1: To elucidate the molecular mechanism(s) of MiT/TFE regulation in the context of epidermal *Tsc1* and *Raptor* loss. Aim 2: To study the expression of MiT/TFEs and lysosomal genes in human and murine AML and *TSC1/2*-related RCC and the role of lysosomal biogenesis in renal tumors driven by TSC1/2 loss.
Projects Overlap or Parallel: no scientific or budgetary overlap

What other organizations were involved as partners?

Organization Name: University of California San Francisco

Location of Organization: San Francisco, CA

Partner's contribution to the project

Collaboration : Dr. Felix Feng is a radiation oncologist who will contribute to interpretation of the RTOG9601 data as it is ascertained. He is in charge of the GU Translational Research Program at NRG. Dr. Feng helped with approvals through NRG and with interpretation of the data.

Organization Name: Dana Farber Cancer Institute

Location of Organization: Boston, MA

Partner's contribution to the project

Collaboration : Dr. Chris Sweeney is an oncologist who was PI of the ECOG3805 trial. He is assisting with data interpretation and analysis.

7. SPECIAL REPORTING REQUIREMENTS

Nothing to report

8. APPENDICES: None