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<b>14. ABSTRACT</b> As a member of the Department of Defense Prostate Cancer Clinical Trials Consortium (PCCTC), UCLA has completed its second year as a member. We have opened and enrolled on existing PCCTC trials. Importantly, we have offered and opened one study that has already been activated in the PCCTC. We have offered 5 studies to the PCCTC, of which four are investigator initiated and have been funded by PCF Challenge Awards (n = 3) or an industry sponsor. These studies leverage the results from pre-clinical studies conducted at UCLA, including data generated from the UCLA SPORE and the Stand Up 2 Cancer West Coast Dream Team. The clinical trials offered to the PCCTC by UCLA directly address <b>PCRPs overarching challenges and focus areas</b> . For example, our therapeutic intervention study of oligometastatic disease seeks to identify the molecular profile of primary tumors that ultimately metastasize and thereby <b>distinguish aggressive from indolent disease in men newly diagnosed with prostate cancer</b> . Insight into the drivers of metastasis could lead to the identification of actionable targets <b>to prevent progression to lethal prostate cancer</b> . In leveraging the discoveries generated from the SPORE, SU2C WCDT and other programs, our proposed trials promise to validate novel agents that target specific pathways and combinatorial treatments to improve the <b>therapy</b> of patients with advanced disease.					
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## **INTRODUCTION**

The Departments of Medicine and Urology at the David Geffen School of Medicine at UCLA are notable for the breadth and depth of prostate cancer translational research activities, and for the leadership and multidisciplinary expertise of its investigators and administrative support staff. Both the PI (**Matthew Rettig, M.D.**) and Co-PIs (**Robert Reiter, M.D., Allan Pantuck, M.D., M.D.**) as well as many of the co-investigators (e.g. **Fairooz Kabbinavar, M.D., Arie Beldegrun, M.D., and Mark Litwin, M.D., MPH, William [Bill] Aronson, M.D.**) for this grant proposal have extensive experience with developing and conducting investigator initiated, multi-institutional clinical trials of innovative treatment approaches that have focused on the translation of basic into clinical research. Current prostate cancer recruitment statistics at UCLA demonstrate an adequate population base to meet consortium requirements regarding patient accrual. Moreover, a close affiliation with the West Los Angeles VA, located about than one mile from the UCLA hospital, will markedly enhance our recruitment of veteran and minority, especially African-American, populations.

The renewal of the UCLA Prostate Cancer SPORE and its associated infrastructure has greatly enhanced the ability of the UCLA DOD Consortium Research Site to execute early phase clinical trials. In order to achieve the fullest impact within the DOD program, the UCLA site will interface internally with the UCLA Prostate Cancer SPORE. As PI of the SPORE, Dr. Robert Reiter, who is a co-PI of this proposal, will be able to leverage support from the SPORE to facilitate a mutually beneficial interaction between the UCLA DOD site and the SPORE infrastructure. Specifically, access to the SPORE Pathology, Administrative, Imaging, and Biostatistics and Biomathematics Cores will facilitate the successful completion of clinical studies. There is also potential for the SPORE to benefit from interactions with the DOD Consortium. In particular, SPORE translational studies that are currently focused at UCLA can be presented to the Consortium for consideration. In addition, as a member of the Stand Up 2 Cancer West Coast Dream Team and one of the two lead sites for this program, we have experience in collaborating in this multi-institutional project to define the adaptive pathways of resistance in mCRPC patients who have progressed on enzalutamide and/or abiraterone. In fact, Dr. Rettig has leveraged the data from this study to design a clinical trials\ aimed at inhibiting/targeting key pathways which are hyperactivated in these patients. This studies, described below, has been approved for funding and has been approved for pending activation in the PCCTC. Importantly, we have included physicians in training and junior faculty in the development of new protocols. These investigators include members of the Hematology-Oncology Division and the Department of Radiation Oncology.

**KEY WORDS:** 1) prostate cancer, 2) castration resistant, 3) DNA damage repair genes, 4) Mitogen activated protein kinase MAPK, 5) stereotactic body radiation therapy, 6) oligometastatic

## **ACCOMPLISHMENTS:**

### **Major Task 1. Adhere to performance metrics defined by Coordinating Center**

**Subtask 1.** Accrue at least 25 patients per year to PCCTC trials.

A total of 81 patients were enrolled during the three year duration of the award.

**Subtask 2:** Accrue at least 5% of patients from disproportionately affected populations per year.

Of the 81 patients accrued to date, 13 are from minority or disproportionately affected populations (Hispanic = 3; African American = 10). **Importantly, the potential to enhance recruitment of minority populations, especially African American patients, was facilitated by the integration of the of a nascent VA-PCF Precision Oncology Program in Cancer of the Prostate (POPCAP). The POPCAP mission is aimed at bringing precision medicine to Veterans with prostate cancer; the program, to which the PCF has publicly committed \$50,000,000 over the next five years, is an official component of Vice President Biden’s Cancer Moonshot. Dr. Rettig has been appointed as co-chair of the POPCAP Steering Committee. As an immediate goal of this VA-PCF program, VA sites that are affiliated with PCCTC academic centers (e.g. UCLA, University of Washington, UCSF, OHSU, etc) will participate in biomarker driven phase 2 clinical trials. As the co-chair of the POPCAP Steering Committee, Dr. Rettig has spearheaded the initiation of clinical trials funded by the PCF that are being conducted at multiple VA sites. Given that prostate cancer is the most frequently diagnosed malignancy (other than non-melanoma skin cancers) amongst our Veterans, represents ~1/3 of all cancer diagnoses in the Veteran population nationwide, and disproportionately affects African American Veterans, we fully anticipate that the nascent POPCAP program will significantly enhance the recruitment of minority and disproportionately affected populations to PCCTC studies.**

**Subtask 3.** . Propose  $\geq 2$  clinical trials per year or 6 trials over 3 years for consideration by the consortium, which may include biomarker studies.

During the first two years of our award, we have proposed four studies:

- “Randomized, Open-Label, Neoadjuvant Phase 2 Study Comparing the Effects of AR Inhibition with and without SRC or MEK Inhibition on the Development of EMT in Prostate Cancer.” This study is an investigator initiated study that is funded by a PCF Challenge Award (Reiter = PI,

Rettig = co-PI). Other PCCTC site = University of Washington. The rationale for this study originated from pre-clinical studies supported by the UCLA Prostate Cancer SPORE.

- Status: Closed to accrual; accrual = 45 total.
- “A Single-Arm, Open-Label, Two-Stage Phase II Study of the MEK 1/2 Inhibitor Trametinib in Men with Progressive Metastatic Castrate Resistant Prostate Cancer.” This is funded by a PCF Challenge Award (Rettig = PI) and Novartis is providing the study drug. This work is premised on pre-clinical studies funded by the SPORE and the SU2C WCDT and was presented at the PCF Annual Scientific Retreat in 2015 by Dr. Rettig. UCSF and Dana Farber Cancer Institute = PCCTC sites. Please see below, **Completed, Ongoing and Potential Phase 2 Studies** section for more details.
  - Status: Open and enrolling (n = 6).
  - Pending initiation at UCSF (Ryan) and DFCI (Sweeney).
- “A Phase 1/2, Open-Label, Uncontrolled, Multiple-Dose Escalation, Cohort Expansion and Extension Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of ASN001 in Subjects with Metastatic Progressive Castrate Resistant Prostate Cancer.” This study, led by Dr. Pantuck, is assessing the clinical effects of a relatively selective 17,20 lyase inhibitor.
  - Status: Open at UCLA; accrual = 2 in current year.
- “A Single-Arm, Open-Label, Phase II Study of Systemic and Tumor Directed Therapy for Newly Diagnosed Oligometastatic M1 Prostate Cancer.”
  - Status: Study was recently opened and is currently recruiting. Please see **Potential Studies to be Considered for the DOD Consortium** section for more details. PCCTC sites = UCLA, WLA VA, UW.
- “A Phase 2 Study of Docetaxel and Carboplatin for Treatment of Patients with Metastatic, Castration Resistant Prostate cancer and Germline or Somatic DNA Repair Deficiency.”
  - Status: Open to enrollment: 15 patients enrolled. This study will be performed in the VA system in VAs associated with PCCTC member institutions and leverages the relatively new insight into the high frequency of inactivating mutations of DNA repair genes in patients with metastatic prostate cancer. This study will provide the proof-of-principle evidence that biomarker driven studies are entirely feasible in the VA system and will facilitate the inclusion of disproportionately affected populations, especially African Americans who are highly represented in the VA prostate cancer population. Study is funded by a PCF Challenge Award (Rettig = PI).

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**Subtask 4.** *Participate as a Clinical Research Site in  $\geq 6$  trials initiated by other sites.* In addition to the four studies that we have offered to the PCCTC, we have opened the following studies offered by other PCCTC sites:

- “A Single-arm, Phase 2 Study to Evaluate the Safety and Efficacy of VT-464 in Patients with Castration-Resistant Prostate Cancer Progressing on Enzalutamide or Abiraterone.”
  - Status: Open at UCLA; accrual = 5 total.
- “Identifying Mechanisms of Resistance to Enzalutamide (MDV3100) Treatment in Men with Castration-Resistant Prostate Cancer.”
- “**Zenith 1:** A Phase 1 Safety and Tolerability Study of ZEN003694 in Patients with Metastatic Castration-Resistant Prostate Cancer.”
  - Status: Closed to accrual. Enrolled 3 patients.
- “**Zenith 2:** A Phase 1 Safety and Tolerability Study of ZEN003694 in Combination **with Enzalutamide** in Patients with Metastatic Castration-Resistant Prostate Cancer.”
  - Status: Open at UCLA (August, 2016); actively recruiting; enrolled 1 patients.
- c16-168: BRCAAway: A Randomized Phase II Trial of Abiraterone, Olaparib, or Abiraterone + Olaparib in Patients with Metastatic Castration-Resistant Prostate Cancer with DNA Repair Defects.
  - Status: Local regulatory approval obtained. Awaiting execution of contract/budget.
- Randomized phase IB/II study of enzalutamide with and without ribociclib in patients with metastatic castrate resistant, chemotherapy naïve prostate cancer that retains RB expression
  - Status: undergoing regulatory approval and contract execution.
- DORA Trial: Phase III Trial of Docetaxel vs. Docetaxel and Radium-223 for Metastatic Castration-Resistant Prostate Cancer (mCRPC).
  - Status: undergoing regulatory approval and contract execution.
- Identifying Mechanisms of Resistance to Enzalutamide (MDV-3100) Treatment in Men with Castration-Resistant Prostate Cancer.
  - Status: Closed to accrual. Enrolled 4 patients.

## **Major Task 2. Full participation in the consortium as a member of the Clinical Consortium Committee/Scientific Oversight Committee**

- **Subtask 1.** *Participate in  $\geq 1$  PCCTC committee.* As PI, Dr. Rettig is a member of and has fully participated in the PCCTC Scientific Oversight Committee. For example, Dr. Rettig attends the in person meetings of the Committee and the EAB.
- **Subtask 2.** *Attend all face-to-face meetings of the PCCTC.* Dr. Rettig attends all face-to-face meetings (e.g. meetings at GU ASCO and PCF Annual Retreat). In the uncommon circumstance when Dr. Rettig has a conflict, another representative of the UCLA program attends the meeting (e.g. ASCO 2016, Nicholas Nickols, MD, PhD.).
- **Subtask 3.** *Participate in scheduled consortium conference calls.* There is consistent UCLA representation on the monthly teleconferences. Dr. Rettig has personally attended all teleconferences; other UCLA attendees have included Dr. Pantuck and Dr. Nickols.
- **Subtask 4.** *Participate in review meetings/evaluation by the External Advisory Board (EAB).* Dr. Rettig attended the EAB meetings in throughout the course of the period of the grant.
- **Subtask 5.** *Compliance with the operations manual of the Consortium.* UCLA has complied with all aspects of the operations manual, including:
  - Publication of major findings,
  - Intellectual and material property issues,
  - Quality assurance and control procedures,
  - Data submission and management plans.

### **IMPACT:**

UCLA's prostate cancer research program has a long track record of translational research, manifest in the recent renewal of its prostate cancer SPORE. UCLA's program led to the development of PSCA (Dr. Reiter) and Medivation's new androgen receptor antagonist (Drs. Charles Sawyers and Michael Jung). Current programs are aimed at development of new imaging agents and additional targeted agents in prostate cancer. The short-term impact of the UCLA Consortium Site will enhance:

1. the recruitment of patients, especially minority and disproportionately affects populations through the VA-PCF partnership known as POPCAP;
2. the understanding of the drivers of lethal and metastatic prostate cancer, and

3. the execution of diagnostic and therapeutic clinical trials developed at UCLA and performed in the PCCTC. These leverage the discovery programs in the UCLA Prostate Cancer SPORE, the SU2C WCDT program, and innumerable intramural and extramural collaborations. In particular, these programs are accelerating the development and understanding of new drugs to the clinic and providing larger biotech and pharmaceutical companies with the proof they need to move these drugs into late stage development.

We have enrolled prostate cancer patients across the spectrum of the disease from neoadjuvant therapies prior to definitive local treatments for high risk clinically localized disease to patients with therapy resistant mCRPC. Through access to unique programs at UCLA, including the IMPACT program and POPCAP, we have included a relatively high proportion of men from minority and disproportionately affected patient populations. The goals of the consortium also synergized well with other extant programs at UCLA, particularly the SPORE, the POPCAP program, and the SU2C WCDT. Finally, UCLA's track record in translational and clinical research has provided expertise and promising new agents to the consortium, with mutual benefits to all. Thus, the long-term impact of this translational research program will improve diagnostics, imaging agents, biomarkers of response/resistance, and targeted agents for specific prostate cancer subsets so as to eliminate death and suffering from prostate cancer and to enhance the well-being of men experiencing the impact of the disease through the development of more effective methods for its diagnosis, prevention, and treatment.

The clinical trials offered to the PCCTC by UCLA directly addressed PCRP overarching challenges and focus areas. For example, our therapeutic intervention study of oligometastatic disease seeks to identify the molecular profile of primary tumors that ultimately metastasize and thereby distinguish aggressive from indolent disease in men newly diagnosed with prostate cancer. This goal is achieved by collecting metastatic tissue and radical prostatectomy specimens *prior* to any treatment intervention so that correlations between the molecular profile of the multiple primary tumors in any one prostatectomy specimen with that of a metastatic lesion can be performed. Insight into the drivers of metastasis could lead to the identification of actionable targets to prevent progression to lethal prostate cancer. Moreover, the selection of clinical trials that incorporate pre-treatment and post-treatment biopsies to test the effect of specific targeted agents (e.g. trametinib) in mCRPC patients will facilitate the development of effective treatments and address mechanisms of resistance for men with high-risk or metastatic prostate cancer as well as identify biomarkers of response and resistance. In leveraging the discovery generated from the SPORE, SU2C WCDT and other programs, the proposed trials promise to validate novel agents that target specific pathways and combinatorial treatments to improve the therapy of patients with advanced disease.

As a member institution of the PCCTC, we feel that we have impacted progress into the understanding and improvement in clinical outcomes of men with prostate cancer, especially mCRPC. Our neoadjuvant study, which has completed accrual and is undergoing data analysis and correlative studies, seeks to determine whether ADT itself activates pathways that can actually trigger progression and metastasis. Specifically, we will determine if ADT activates SRC and MAPK pathways and if inhibition of these pathways is effective in patients undergoing neoadjuvant treatment prior to radical prostatectomy. The results of this study may have critical implications not only for patients with clinically localized, high risk prostate cancer but also mCRPC. This work dovetails with one of the studies that we have proposed to the PCCTC: "A single-arm, open-label, two-stage phase II study of the MEK 1/2 inhibitor trametinib in men with progressive metastatic castrate resistant prostate cancer." This study is premised on our recent findings presented by Dr. Rettig at the PCF Annual Retreat that the MAPK pathway is the mostly highly activated signal transduction pathway in mCRPC patients who have progressed on abiraterone and/or enzalutamide. This study has been approved for funding by the PCF in the form of a Challenge Award and Novartis has agreed to provide trametinib; it is open to enrollment (n =6 so far). Our study of platinum based chemotherapy for mCRPC patients with germline mutations in DNA damage repair genes builds on the results of recent reports demonstrating the high frequency of these mutations; this study is open and is being conducted in the VA system and will result in the accrual of a relatively high percentage of African Americans.

These investigator-initiated studies that leverage the pre-clinical and patient related data are ideal approaches to translational science that can improve the quality and quantity of life of prostate cancer patients.

**CHANGES/PROBLEMS:**

We have not encountered any specific problems. Dr. Reiter replaced Dr. Rettig as the PI of the neoadjuvant study in order to more equitably share workload. Dr. Nicholas Nickols, MD, PhD, has started to play an active role in the UCLA site. Dr. Nickols, who was a VA Career Development Award 2 investigator and now a PCF Young Investigator under Dr. Rettig's mentorship is the PI of the aforementioned oligometastatic study.

**PRODUCTS:**

None.

**PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

**UCLA:**

Dr. Robert Reiter, Professor of Urology, UCLA. No change.

Dr. Allan Pantuck, Professor of Urology, UCLA. No change.  
Dr. Fairouz Kabbinavar, Professor of Medicine and Urology, UCLA. No change.

**Collaborating Organizations:**

**UCSF and OHSU:** These institutions (Eric Small at UCSF and Tomasz Beer at OHSU) are MAPK protocol and were instrumental in generating the preliminary data for this study. They will be participating in clinical trial execution.

**UC Santa Cruz:** We are working with UCSC for bioinformatics analysis of our MAPK study. UCSC is the principle site for bioinformatics analysis of the SU2C WCDT study, which generated the preclinical data for this study. We are leveraging our relationship with UCSC for our MAPK study.

**University of Washington/Puget Sound VA.** Dr. Bruce Montgomery is Dr. Bruce Montgomery is the PI at these sits for three studies:

- “A Phase 2 Study of Docetaxel and Carboplatin for Treatment of Patients with Metastatic, Castration Resistant Prostate cancer and Germline or Somatic DNA Repair Deficiency.”
- “A Single-Arm, Open-Label, Phase II Study Of Systemic And Tumor Directed Therapy For Newly Diagnosed Oligometastatic M1 Prostate Cancer.”

**Dana Farber Cancer Institute:** Dr. Chris Sweeney will be the site PI for our phase 2 study of trametinib in mCRPC patients.

**SPECIAL REPORTING REQUIREMENTS**

None.

**APPENDICES**

None.