AWARD NUMBER:	W81XWH-18-1-0363
TITLE:	A Combination Study of Durvalumab plus Olaparib in an Unselected Population with Metastatic Castrate-Resistant Prostate Cancer (mCRPC)
PRINCIPAL INVESTIGATOR:	Fatima Karzai, MD
CONTRACTING ORGANIZATION:	The Geneva Foundation 917 Pacific Ave. Suite 600 Tacoma WA 98402
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PREPARED FOR:	U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012
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6. AUTHOR(S)
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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Data suggest that 25%–30% of sporadic metastatic castration-resistant prostate cancers (mCRPC) have defects in DNA repair pathways that may confer sensitivity to PARP inhibition. Next generation sequencing (NGS) has identified recurrent mutations and genomic alterations in mCRPC that are potentially clinically actionable, including mutations in DNA damage response factors BRCA2, BRCA1 ATM and/or CHK2. Recent data indicate that DNA damage plays an important role in priming a type I interferon (IFN) response, where DNA damage results in enhanced production of type I IFNs via the cytosolic DNA sensor STING, which can prime the innate and adaptive immune system for an amplified response. While programmed cell death protein ligand 1 (PD-L1) inhibition has shown antitumor effects in bladder and non-small cell lung cancers and melanoma, immune checkpoint blocking antibodies have had limited success in mCRPC. It is likely that immune combination strategies are required to improve response rates in prostate cancer beyond <10% seen with immune checkpoint inhibitors alone. We hypothesize that increased DNA damage by the PARP inhibitor olaparib will complement the antitumor activity of durvalumab, an anti-PDL-1 antibody, in an expansion cohort of a phase II study of men with mCRPC in the post-enzalutamide and/or abiraterone setting.

15. SUBJECT TERMS

NONE LISTED

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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1. Introduction

Two recent FDA approvals have expanded the role of targeted therapies for men with metastatic castration-resistant prostate cancer (mCRPC) with DNA damage repair (DDR) mutations. In May 2020, the PARP inhibitor olaparib was approved for men with deleterious or suspected deleterious germline or somatic DDR mutations who have progressed on treatment with enzalutamide and/or abiraterone based on the phase III PROfound study. In Cohort A (men with mutations in *BRCA1*, *BRCA2* or *ATM*), rPFS was improved with olaparib vs. investigator's choice of enzalutamide or abiraterone, with a median of 7.4 months vs. 3.6 months (p<0.0001) with a median OS of 19.1 months vs. 14.7 months (P=0.0175). Similarly, another PARP inhibitor, rucaparib, was FDA accelerated approval in May 2020 in men with mCPRC with *BRCA1/2* mutations based on the phase II TRITON2 study that showed an improved ORR rate. While these approvals provide additional treatment options for men with DDR mutations, there are multiple mechanisms of PARP resistance leading to limiting benefit of therapy and other routes, particularly combination therapies, need to be explored.

While immune checkpoint inhibitors have shown great promise in solid tumors such as melanoma, bladder and non-small cell lung cancer, single agent studies in prostate cancer have not been successful except in a small subset of patients. Again, rationale combination treatment regimens may improve the role of immune checkpoint blockade in mCRPC. Possible mechanisms of action can be synergistic or additive. One such mechanism may be release of damaged DNA into the cytosol via PARP inhibition which activates an immune pathway called cGAS–STING. In this phase II study, the combination of the PARP inhibitor, olaparib, plus an anti-PD-L1 immune checkpoint inhibitor, durvalumab, is given to men with mCRPC after previous treatment with enzalutamide and/or abiraterone. Durvalumab is given at 1500 mg iv q28 days plus olaparib 300 mg tablets po q12 hours. The primary endpoint is PFS. Core biopsies undergo mutational analysis.

2. Keywords

Metastatic, prostate cancer, PARP inhibitors, immunotherapy, immune checkpoint blocking antibodies, DNA damage repair, mutations

3. Accomplishments

Major Goals and Accomplishments:
Over the course of the grant period, we have accomplished the following, according to the tasks laid out in the original SOW:

Task 1: Submit protocol to NCI IRB and HRPO and obtain approval(s) for expansion cohort:

Completed.

Task 2: Analyze potential biomarkers of response, including genomic, proteomic, and immunologic correlates from tumor biopsies and blood samples:

A total of 56 patients have accrued to the trial and 54 on-study biopsies have been attempted.

Task 3: Data Analysis and Preparation:

The trial has accrued 56 patients with a median age of 64 years old (45-88 years). Median baseline PSA was 67 (0.02-5000 ng/mL). Twenty-five patients (46%) had bone disease, 16 (28%) with bone/soft tissue disease, and 12 patients (24%) with bone/soft tissue and visceral disease. One patient (2%) had soft-tissue disease only. Seventy-four percent of patients had prior enzalutamide with 43% of patients having been treated with both enzalutamide and abiraterone. Approximately half of patients had had prior chemotherapy with docetaxel. The most common treatment-related grade 3 or 4 adverse events were anemia, fatigue, and nausea. Patients with immune-related adverse events of any grade include 2 patients with acute onset unilateral hearing loss, optic neuritis, remitting seronegative symmetrical synovitis with pitting edema, insulin-dependent diabetes and colitis in a patient, and enteritis.

Task 4: Training Plans:

Results will be published when the trial is closed to accrual (projected 2021), with up to 65 patients. Upon completion of accrual, final correlative analyses (genomics, serum, immune correlates, etc). will be initiated with NCI collaborators and plans for publication will begin (projected 2021/22). Additionally, a follow-up protocol based on the results of this study will be brought forth for scientific consideration.

4. Impact:

Twelve patients had mutations (germline and/or somatic) in *BRCA2* with PSA declines ranging from +6% to -99%. One patient with a germline *NBN* mutation has a sustained maximal PSA decline of -99% for over 2 years. Of 56 patients, 5 patients have a partial response by RECISTv1.1. Sustained PSA declines of >90% was seen in 5 patients. Median PFS in *BRCA2* mutated patients is 16.5 months (95% CI: 7.7-24.7 months). In patients with no known mutations in DDR pathways, median PFS is 4.8 months (95% CI: 3.0-6.4 months). The median OS has not been reached for patients with *BRCA2* mutations, but 24-month OS is 64.8% (95% CI: 31.0-85.2%) in comparison to 15.0 months in patients with no known DDR mutations [24-month OS: 12.1% (95% CI: 2.0-31.6%)].

5. Changes/Problems:

During the pandemic, clinical trial accrual to NCI studies, including this study, has fallen dramatically. Important research collaborators have closed their labs and stopped their experiments which has impacted correlative studies. Additional, services such as Interventional Radiology, have halted research biopsies. Unfortunately, due to the COVID-19 pandemic, 2 patients have been enrolled that we were unable to obtain biopsies on secondary to cessation of research procedures for safety.

6. Products:

None

7. Participants and Other Collaborating Organizations:

Name:	Fatima Karzai, MD
Project Role:	Principal Investigator
Researcher Identifier:	
Nearest person months worked:	12.00
Contribution to the project:	Overseeing the project as PI and leading the effort.

Name:	James Gulley, MD, PhD
Project Role:	Mentor
Researcher Identifier:	
Nearest person months worked:	12.00
Contribution to the project:	Mentor and consultant to Dr. Karzai

Changes in active support: Nothing to Report

8. Special Reporting Requirements

Quad chart and award chart attached

9. Appendices

None

PC171052: A Combination Study of Durvalumab plus Olaparib in an Unselected Population with Metastatic Castrate-Resistant Prostate Cancer

PI: Fatima Karzai, MD, NCI, Maryland

Budget: $225,896.00

Topic Area: Prostate Cancer Research Program

Mechanism: W81XWH-17-PCRP-PRA

Research Area(s): Oncology

Award Status: 8/1/2018 through 7/31/2022

Study Goals:

1. To determine the response rate of olaparib plus durvalumab in non-DNA damage repair (DDR) mutated mCRPC as measured by PFS and secondarily, as measured by PSA and imaging.
2. To analyze potential biomarkers of response, including genomic, proteomic and immunologic correlates from paired tumor biopsies and blood samples.

Specific Aims:

- Specific Aim 1: Clinical Trial of Olaparib plus Durvalumab-Expansion Cohort
- Specific Aim 2: Analysis of tumor biopsies and blood samples

Key Accomplishments and Outcomes:

Publications: Karzai F, VanderWeele D, Madan RA, et al. Activity of durvalumab plus olaparib in metastatic castration-resistant prostate cancer in men with and without DNA damage repair mutations. J Immunother Cancer. 6(1): 141, 2018.

Patents: None to date

Funding Obtained: $225,896.00

"A Combination Study of Durvalumab plus Olaparib in an Unselected Population with Metastatic Castrate-Resistant Prostate Cancer"

PC171052

W81XWH-18-1-0363

PI: Fatima Karzai, M.D. **Org:** The Geneva Foundation **Award Amount:** $225,896.00

Study/Product Aim(s)

1. To determine the response rate of olaparib plus durvalumab in non-DNA damage repair (DDR) mutated mCRPC and in patients with DDR mutations as measured by PFS and secondarily, as measured by PSA and imaging.
2. To analyze potential biomarkers of response, including genomic, proteomic and immunologic correlates from tumor biopsies and blood samples.

Approach

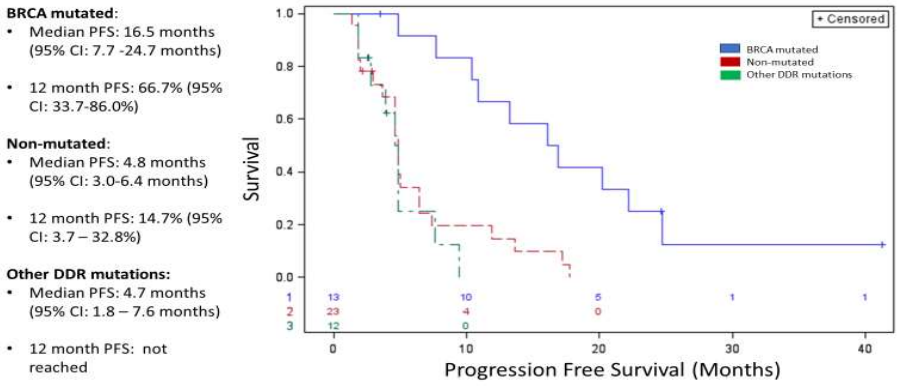
This trial evaluates durvalumab and olaparib in patients with mCRPC with and without somatic or germline DDR mutations. Correlative studies, including genomic and immune assays, will provide data that can be used to provide information on the mechanism of action and provide data for the development of predictive biomarkers in future studies.

Timeline and Cost

Activities CY	19	20	21	22
Submit protocol to NCI IRB and HRPO and obtain approval(s) for expansion cohort: Completed and accrued 56 patients.				
Analyze potential biomarkers of response, including genomic, proteomic, and immunologic correlates from tumor biopsies and blood samples: Began analysis in the first 17 patients.				
Data Analysis and Preparation: Published findings and continue analysis in remaining patients.				
Training Plans: Continue as prior with mentor.				
Estimated Budget ($226K)	**$56K**	**$56K**	**$56K**	**$56K**

Updated: 8/25/2020

Progression Free Survival (PFS)



Accomplishments: (1) Accrued 56 patients to the prostate cohort with anticipation of completion of accrual in 2021. (2) Continue analysis of genomic, proteomic and immunologic correlates

Goals/Milestones

CY20 Goal –Accrual

☐ Complete accrual of approximately 65 patients by early 2021. Attempt to obtain on-study biopsies on all patients. If not feasible, obtain tumor blocks from original biopsies or prostatectomy.

CY21 Goals – Data accumulation

☐ Begin to analyze remaining samples of PBMCs, CTCs, genomics, and immune subsets. Attempt analyses of reversion mutations in DDR genes.

☐ Begin manuscript

☐ Begin letter of intent and protocol writing of a protocol based on current findings.

CY22 Goal –Data Preparation and Analysis

☐ Publish findings

Comments/Challenges/Issues/Concerns: Patient accrual has decreased secondary to the COVID-19 pandemic.

Budget Expenditure to Date

Projected Expenditure (through 8/31/2020): $30,787.26

Actual Expenditure (through 8/31/2020): $30,787.26