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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. Nextgeneration 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 the <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

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1. Introduction

Despite success in other solid tumors, checkpoint inhibitors have not shown overall improvements in survival as monotherapy for metastatic castration-resistant prostate cancer (mCRPC). Two phase III trials of ipilimumab failed to meet their endpoint of improved overall survival. Despite this, there were signs of activity, suggesting that a subset of patients may benefit from immunotherapy. Results from patients previously treated with enzalutamide suggest that enzalutamide may increase expression of programmed death ligand 1 (PD-L1). Indeed, in a separate ongoing trial, 3/12 patients who previously progressed on enzalutamide had objective radiographic responses to programmed cell death protein 1 (PD-1) blockade with pembrolizumab, and 5/28 patients had a prostate-specific antigen (PSA) decline of ≥50%. Mutations in mismatch repair (MMR) genes, one of many pathways involved with DNA damage repair (DDR), are associated with microsatellite instability in advanced prostate cancer and may serve as a possible biomarker of response to immune-blocking antibodies, as seen in other solid tumors. MMR mutations, however, are thought to occur in < 5% of prostate cancer patients. Mutations in other DDR genes appear to occur much more frequently. These include alterations in the homologous recombination repair pathway genes, including BRCA2 and ATM, among others. Alterations in these additional DDR-related genes occur in approximately 20–25% of mCRPC patients, with approximately 12% harboring germline alterations in DDR genes. Mounting evidence from trials in other solid tumors suggests alterations in DDR genes beyond the MMR pathway may also predict response to immunotherapy. There is also increasing rationale for combining PARP inhibition with immunotherapy, even though the mechanism of synergy is not fully understood. Foremost among candidate intracellular pathways is STING (stimulator of interferon genes), an innate immune response activated by cytosolic DNA (perhaps a consequence of DNA damage) that can lead to enhanced interferon (IFN) production. It is evident that, in some patients, mutational burden is associated with response to PD-1/PD-L1 inhibition. It has been suggested that PARP inhibition can potentiate DNA damage and inefficient repair in tumors, and could lead to immunologically relevant mutations.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. In phase I of this study, durvalumab was safely given every 4 weeks at a fixed dose of 1500 mg i.v. in combination with 300 mg of olaparib tablets p.o. every 12 h. This regimen was selected for further study in the phase II cohorts.

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

Expansion cohort has been approved and accruring per NCI IRB and HRPO.

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

A total of 49 patients have acurred to date. All patients have undergo mandatory on-study biopsy. To date, an analysis of the first 17 patients has been completed.

Task 3: Data Analysis and Preparation Seventeen patients with mCRPC who were previously treated with enzalutamide and/or abiraterone were enrolled and treated with durvalumab plus olaparib. Five patients had bone-only disease; 12 had bone and soft tissue/visceral disease. Of the 17 patients, 16 (94%) had received enzalutamide and 11 (65%) had received abiraterone. Ten patients (59%) had previously received both enzalutamide and abiraterone. Eleven patients (65%) had prior chemotherapy for metastatic disease. Seven patients (41%) had prior vaccine therapy (2 had prior PROSTVAC, 4 had prior sipuleucel-T, and one

had both). The most common treatment-related grade 3 or 4 adverse events were anemia (4/17; 24%), lymphopenia (2/17; 12%), infection (2/17; 12%), and nausea (2/17; 12%). Four patients had immune-related adverse events (irAEs) of any grade, including 2 with acute onset unilateral hearing loss, one with optic neuritis, and one who developed remitting seronegative symmetrical synovitis with pitting edema (RS3PE). All irAEs were treated with high-dose steroids. Symptoms improved to near complete resolution with high-dose steroids in the patient with optic neuritis and one patient with acute onset unilateral hearing loss, and to complete resolution in the patient with RS3PE. The second patient with acute onset unilateral hearing loss required use of a hearing aid. Durvalumab was discontinued in all patients who developed irAEs, but olaparib was continued. No patients were taken off-study due to toxicity. Patients received a median of 7 cycles of treatment (range: 2–17).

Nine of 17 patients (53%) had a PSA decline of ≥50% (defined as responders). Of those 9 patients, 4 had a radiographic response per RECIST v.1. For all patients, the 12-month PFS is 51.5% (95% CI: 25.7–72.3%). The median radiographic progression-free survival (rPFS) of patients with alterations in DDR genes was 16.1 months (95% CI: 7.8–18.1 months), with 12-month PFS probability of 83.3% (95% CI: 27.3–94.5%) compared with a 12-month probability of 36.4% (95% CI: 11.2–62.7%) for those without mutations; exact p = 0.031.

Patients' baseline fraction of myeloid-derived suppressor cells (MDSCs) correlated with response to therapy. Patients whose percentage of MDSCs among total viable cells at baseline was ≤ the median had prolonged PFS (p = 0.041). As with multiple chemotherapy trials, circulating tumor cell (CTC) response was an early predictor of benefit for this immunotherapy trial. EpCAM+ CTCs were assessed at cycle 1 day 1 (C1D1), C1D15, and C3D1 in all 17 patients. Baseline CTCs varied among the 17 patients (0–2107 cells/10 mL of blood). The CTC count decreased or was unchanged in response to therapy in 13/17 patients (76%) at C1D15 and in 12/17 patients (71%) at C3D1. Patients with no change or a decrease in CTCs from C1D1 to C1D15 in response to treatment had prolonged PFS compared with those in whom CTCs increased.

Changes in CD8+ and CD4+ cell populations also predicted response. Patients with > median percentage of Ki67+PD-1+ cells among total CD8+ T cells in response to therapy had prolonged PFS, as did patients with > median percentage of Ki67+PD-1+ cells among total CD4+ T cells. Analysis of expression of HLA-DR, another T-cell activation marker, showed that patients with > median percentage of Ki67+HLA-DR CD8+ and CD4+ T cells at C3D1 had prolonged PFS.

Using a sequencing panel targeting 500 cancer-associated genes, we performed genomic analysis of germline DNA for all patients and tumor DNA for 14/17 patients. Four responders harbored germline alterations in DDR genes: one with a known deleterious mutation in *NBN* and 3 with frameshift indels in *BRCA2*. The patients with germline *BRCA2* indels had tumor tissue available which demonstrated somatic deletion of the second allele. Two additional responders had homozygous somatic alterations in *BRCA2*: deletion of one allele and the second allele affected by deleterious nonsynonymous mutation or deletion. One patient also harbored a frameshift indel of *PMS2*, an MMR gene, though the second allele appeared to be intact and there was no evidence of a hypermutation phenotype. Twoother responders had no detected DDR gene biomarker of response. Of these two, one had shallow loss of *BRCA2* with no alteration detected in the other allele, and one had no tumor tissue available for analysis. Three patients have ongoing responses of > 12 months: one with a germline *NBN* mutation, one with somatic deletion of both copies of *BRCA2*, and one with germline indel in *BRCA2* and somatic loss of the remaining allele.

Task 4: Training Plans

Dissemination of Results: Results will be published when the trial is closed to accrural and immune correlatives have been analyzed.

Plans for Next Reporting Period: Complete accrural in 2020 and begin final data analysis.

4. Impact

The preliminary PFS data and response rate for this cohort of mCRPC patients treated with durvalumab

plus olaparib indicate deep and sustained responses with this therapy combination, with 53% of patients having radiographic and/or PSA responses, median PSA decline of 85% among the 9 responders, and median duration of response of 16.1 months in those patients with mutations in DDR genes. One third of responders harbored germline mutations in DDR genes, one third had detectable biallelic somatic alterations in DDR genes, and one third had neither. Mutational burden, DDR status, prior therapies, and other variables can critically affect the cancer-immune set point, the peripheral immune phenotype, and response to therapy. The data suggest that durvalumab plus olaparib can affect both innate and adaptive immunity in patients with mCRPC, and that engagement of these 2 types of immunity may be associated with prolonged PFS. Our data also suggest that durvalumab plus olaparib for mCRPC may promote dendritic cell (DC) maturation, enhance CD4+ T-cell activity, and reactivate CD8+ T-cell antitumor immunity. The clinical development of inhibitors of PARP and PD-1/PD-L1 has had a substantial impact on the treatment of advanced malignancies. This is the first study to demonstrate activity for the combination of these agents in prostate cancer patients without biallelic inactivation in DDR pathways, and deep responses in patients with known mutations. While the analysis to date is limited by a small patient cohort, the 12-month PFS is 51.5% in patients with advanced metastatic disease, > 50% of whom are taxane-refractory. The future of treatment for mCRPC may take us beyond androgen suppression to combination therapies such as PARP inhibition plus immunotherapy.

5. Changes/Problems:

Paired tumor biopsies are not mandatory on the trial (there is only one mandatory on-study biopsy). Some patients have opted out of a second biopsy.

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

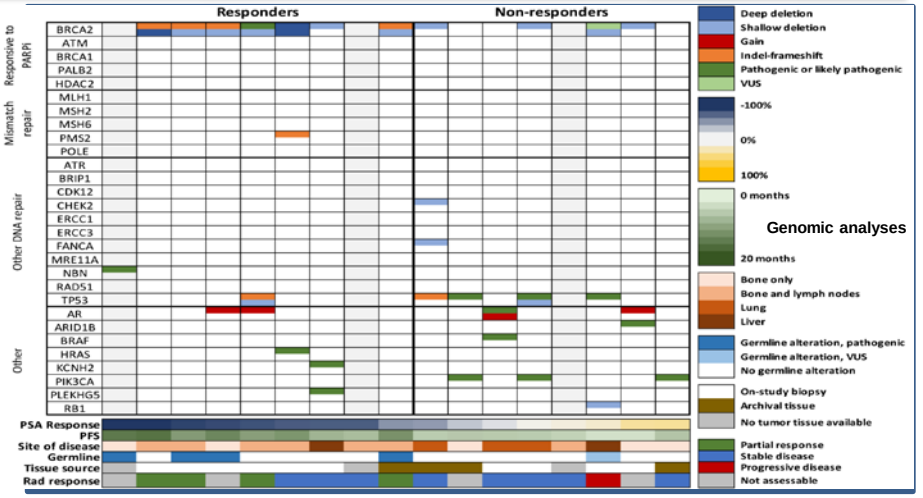
PI: Fatima Karzai, Ph.D. **Org:** The Geneva Foundation **Award Amount:** $225,896.00

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

Checkpoint inhibitors have not been effective for prostate cancer as single agents. Durvalumab is a human IgG1-K monoclonal antibody that targets programmed death ligand 1 and is approved by the U.S. Food and Drug Administration for locally advanced or metastatic urothelial cancer and locally advanced, unresectable stage 3 non-small cell lung cancer. Olaparib, a poly (ADP-ribose) polymerase inhibitor, has demonstrated an improvement in median progression-free survival (PFS) in select patients with metastatic castration-resistant prostate cancer (mCRPC). Data from other trials suggest there may be improved activity in men with DNA damage repair (DDR) mutations treated with checkpoint inhibitors. This trial evaluated 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.



Accomplishments: (1) Accrued 49 patients to the prostate cohort with anticipation of completion of accrual in 2020. (2) Began analysis of genomic, proteomic and immunologic correlates in the firs 17 patients in the cohort. (3) Published findings in JITC.

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 49 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: 12/6/2019

Goals/Milestones (Example)

CY19 Goal –Accrual

☐ Complete accrual of 50 patients by end of 2019. Continue obtaining and analyzing somatic mutations (genomics) on on-study biopsies.

CY20 Goals – Data accumulation

☐ Continue collection of tumor biopsies and blood samples and complete study accrual.

CY21 Goal –Data Preparation and Analysis

☐ Complete somatic mutational analyses on tumor samples. Complete analysis of changes in circulating tumor cell counts and innate and adaptive immune responses via blood samples. Attempt analyses of reversion mutations in DDR genes.

CY22 Goal –Data Analysis and write new protocol based on data obtained from this protocol.

☐ Publish findings

☐ **Comments/Challenges/Issues/Concerns:** None at this time

- **Budget Expenditure to Date**

Projected Expenditure (through 7/31/19): $19,096.60

Actual Expenditure (as of 7/31/19): $37,377.60