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TITLE:	A Combination Study of Durvalumab plus Olaparib in an Unselected Population with Metastatic Castrate-Resistant Prostate Cancer (mCRPC)
PRINCIPAL INVESTIGATOR:	Dr. Fatima Karzai
CONTRACTING ORGANIZATION:	The Geneva Foundation, Tacoma, WA
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6. AUTHOR(S)

Dr. Fatima Karzai
Fatima.karzai@nih.gov

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

The Geneva Foundation
917 Pacific Avenue. Suite 600
Tacoma, WA 98402

8. PERFORMING ORGANIZATION REPORT NUMBER

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Objective: Increased DNA damage by olaparib will complement the antitumor activity of the immune checkpoint blocking antibody durvalumab.
Specific Aims:
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. Impact: Preliminary results from this combination study in an unselected population with mCRPC show robust, sustained PSA findings and objective responses in patients with measurable disease. By using the PD-1/PD-L1 axis as a therapeutic target, in combination with PARP inhibition, regardless of mutational status, we may provide patients a new treatment option. This study may have a broader impact on the development of immunotherapies for all stages of prostate cancer and potentially other immunologically "cold" tumors. Correlative studies, including genomic and immune assays, will provide preliminary 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

15. SUBJECT TERMS
Oncology, Prostate Cancer

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

Checkpoint inhibitors have yielded disappointing results in prostate cancer as single agents, except in a small subset of patients. Durvalumab, a monoclonal antibody, targets programmed death ligand-1 and is approved by the U.S. Food and Drug Administration for locally advanced or metastatic urothelial cancer. Olaparib, a poly (ADP-ribose) polymerase inhibitor, has demonstrated an improvement in median progression-free survival (PFS) and overall survival (OS) in select patients with metastatic castration-resistant prostate cancer (mCRPC) with germline or somatic mutations in DNA damage repair (DDR) mutations BRCA1/2. Data from other trials suggest there may be improved activity in men with DDR mutations treated with checkpoint inhibitors. This trial evaluates durvalumab and olaparib in patients with mCRPC with and without somatic or germline DDR mutations.

2. KEYWORDS:

durvalumab, olaparib, mCRPC, abiraterone, enzalutamide, immunotherapy, anti-PD-L1, PARP inhibitors

3. ACCOMPLISHMENTS:

What were the major goals of the project?

- **Specific Aim 1:** Clinical Trial of Olaparib plus Durvalumab Expansion Cohort
    - **Major Task 1:** Obtain IRB and HRPO approvals-**Completed.**
        a. **Subtask 1**: Enroll and manage patients on clinical trial-**Completed.** This trial accrued a total of 60 patients. One patient remains on active treatment.
        b. **Subtask 2**: Meet with mentor monthly to discuss clinical trial experience and methods to optimize implementation, recruitment and management-**Ongoing**. Monthly meetings with mentor and weekly patient updates with entire Genitourinary Malignancies Branch at the National Cancer Institute.
- **Specific Aim 2:** Analysis of tumor biopsies and blood samples
    - **Major Task 2:** Analyze potential biomarkers of response, including genomic, proteomic and immunologic correlates for tumor biopsies and blood samples. **Ongoing.**
        a. **Subtask 1:** Perform mutational analyses on available tissue specimens- Of 60 patients accrued, biopsy of area of metastatic prostate cancer was attempted on 58 patients. Two patients were unable to have on-study biopsy secondary to COVID-19 restrictions in Interventional Radiology. **Completed**.

b. **Subtask 2:** Circulating tumor cell (CTC) analysis: Ongoing with research collaborator. **Completed.**
c. Subtask 3: Meet with mentor to review data and optimize procedures. Meet with mentor weekly to review patients on protocol returning to clinic for assessment and monthly for data review and progress. **Ongoing.**

- **Major Task 3:** Data Analysis and Preparation.
  a. **Subtask 1**: Evaluate interval data with mentorship team-**Completed.**
  b. **Subtask 2**: Prepare manuscript(s) for publication with mentor-**Manuscript currently in preparation for the complete 60 patient cohort.**

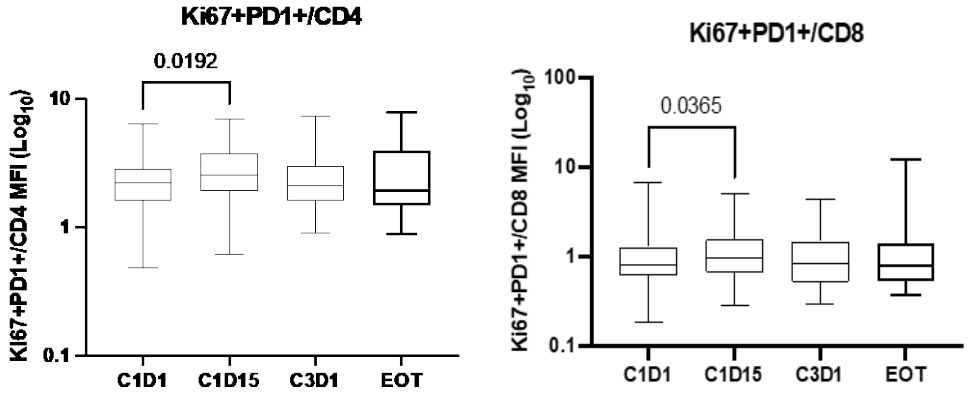
- **Major Task 4**: Training Plans
  a. **Subtask 1:** Meet weekly with mentor to discuss my leadership development and the skills and areas to improve upon in my transition to an independent researcher-My leadership development continues to progress and has been enhanced by leading this protocol cohort. I am currently in discussions for development of a follow-up protocol using olaparib and immunotherapy in advanced prostate cancer where I will the PI of the study. I have been promoted to Associate Research Physician (equivalent to Associate Professor) and Clinical Director of the Genitourinary Malignancies Branch at the NCI, NIH, and I am an independent investigator, and I am the PI of multiple trials. **Ongoing.**
  b. **Subtask 2**: Engage with mentor and collaborators to discuss and present data at scientific seminars. Data from this project was presented as a Merit award winning abstract/poster presentation at ASCO GU 2021. **Completed.**
  c. **Subtask 3**: Attend weekly laboratory meetings in the Laboratory of Tumor Immunology and Biology (now the Center for Immuno-Oncology) to learn about multidisciplinary translational research approaches in immunotherapy. I attend weekly meetings discussing pre-clinical models and drug development. **Ongoing.**
  d. **Subtask 4:** Seek out experts in the fields of immunotherapy and DNA damage repair to discuss findings from this trial to identify possible biomarkers of response and develop strategies for future translational clinical trials. I continue to work with experts in the GU field in both immunotherapy (Mentor: Dr. James L. Gulley), and in women's malignancies in DNA damage repair (Dr. Jung-Min Lee). **Ongoing.**

What was accomplished under these goals?

In this reporting period, a major activity that was accomplished is the completion of accrual to the clinical trial with 60 patients with metastatic castrate-resistant prostate cancer (mCRPC). For specific objectives, we are currently assessing the mutational status of 58 patients on whom biopsies of metastatic sites of disease were attempted. Two patients did not have biopsies because the COVID-19 pandemic shut down the ability to do non-urgent interventions in Interventional Radiology at the NIH. Significant results include circulating tumor cell (CTC) analyses which reveal activated proliferating CD4+ and CD8+ T cells increased after therapy and the increase correlates with improved overall survival (OS), increased effector memory and effector T cells and decreased naïve T cells correlated with better OS, and classical and non-classical monocytes, M-MDSC decreased after therapy. Lower Treg at baseline and increased Treg after therapy correlated with better OS or progression-free survival (PFS).

Immune correlates were evaluated pre and post 2 weeks and 8 weeks of durvalumab plus olaparib therapy in 15 patients. Patients were selected based on sample availability and response and included those with PR (n=4), SD (n=5), and PD (n=6). Serum levels of cytokines and soluble factors were evaluated using commercially available kits per the manufactures' instructions. Cryopreserved peripheral blood mononuclear cells (PBMCs) were examined by multicolor flow cytometry using 30 markers in 4 panels to identify 158 peripheral immune cell subsets following methods previously described. This assay identified 10 parental cell types and 148 refined subsets indicative of their maturation status and function. Serum cytokine and soluble factors, CBCs, and 158 immune subsets were measured in patients before treatment and at 2 and 8 weeks after treatment start. Early trends of increases in several inflammatory markers were detected at 2 weeks post treatment initiation. IFN gamma p=0.008), IL-10 p=0.045), and TNF alpha p=0.023) were elevated after 2 weeks of therapy in greater than 50% of patients, and these increases were sustained after 8 weeks of treatment.

% Ki67+PD1+ cells Increased among total CD4+ and CD8+ T cells at C1D15



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

This project afforded me many opportunities for professional development. As a part of this project, I became a Prostate Cancer Foundation Young Investigator, and was able to discuss my findings at the Prostate Cancer Foundation Retreat prior to the COVID-19 pandemic. As principal investigator, I developed leadership skills, and was able to present at the 2018 ASCO GU conference as an oral abstract presentation.

How were the results disseminated to communities of interest?

The results will be disseminated to communities of interest through the publication of a manuscript.

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

During this next reporting period, I will complete the correlative analyses and finish sequencing. In order to do so, I plan on utilizing the rest of the funds to have my collaborators complete their work.

4. IMPACT:

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

The impact of development in mCRPC is substantial. When this clinical trial began, the relationship between olaparib and patients with mCRPC was unclear, particularly in light of combinations with immunotherapy. This protocol has shown (along with phase III studies of PARPi alone), that patients with *BRCA* mutations benefit the most from the combination therapy.

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.

5. 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

Changes that had a significant impact on expenditures

During the COVID-19 pandemic, clinical trial accrual to NCI studies, including this study, fell dramatically. The capacity of our clinic to sign-on and evaluate patients was significantly reduced. Important research collaborators have significantly reduced their laboratory capabilities which has impacted correlative studies. Additional, services such as Interventional Radiology, halted research biopsies for safety reasons. Unfortunately, due to the COVID-19 pandemic, two patients were enrolled for which we were unable to obtain biopsies of metastatic sites of disease secondary to cessation of research procedures for safety. These problems and delays have resulted in decreased expenditures for collaborative studies and additional time need to complete the correlatives, particularly sequencing, and to complete expenditures.

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

Significant changes in use or care of human subjects

Nothing to report.

Significant changes in use or care of vertebrate animals

Nothing to Report.

Significant changes in use of biohazards and/or select agents

Nothing to report.

6. PRODUCTS:

- **Publications, conference papers, and presentations**

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**

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	*William L. Dahut, M.D., **Changed.***
Project Role:	*Associate Investigator*
Researcher Identifier (e.g. ORCID ID):	*0000-0002-2766-9703*
Nearest person month worked:	*August 2021*
Contribution to Project:	*Mentorship and Associate Investigator*
Funding Support:	*The CRADA between NCI and AstraZeneca*

Name:	*James L. Gulley, M.D., Ph.D, No change*
Project Role:	*Associate Investigator*
Researcher Identifier (e.g. ORCID ID):	*0000-0002-6569-2912*
Nearest person month worked:	*August 2021*
Contribution to Project:	*Clinical Mentorship and Associate Investigator*
Funding Support:	*The CRADA between NCI and AstraZeneca*

Name:	*Helen T. Owens, R.N., No change*
Project Role:	*Research Nurse*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*August 2021*
Contribution to Project:	*Regulatory and Clinical*
Funding Support:	*N/A*

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

Dr. William L. Dahut has retired from federal service and is now a special volunteer at the NCI rather than an associate investigator.

What other organizations were involved as partners?

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

9. APPENDICES: