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:	Dr. Fatima Karzai
CONTRACTING ORGANIZATION:	The Geneva Foundation 917 Pacific Ave #600 Tacoma, WA 98402
REPORT DATE:	August 2021
TYPE OF REPORT:	Annual Report
PREPARED FOR:	U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012
DISTRIBUTION STATEMENT:	Approved for Public Release; Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
August 2021	Annual Report	1 August 2020 – 31 July 2021

4. TITLE AND SUBTITLE

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

5a. CONTRACT NUMBER
W81XWH-18-1-0363

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
The Geneva Foundation
917 Pacific Ave. # 600
Tacoma, WA 98402

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

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
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	13	19b. TELEPHONE NUMBER *(include area code)*

Table of Contents

1. INTRODUCTION: *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

Checkpoint inhibitors have not been effective for 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: *Provide a brief list of keywords (limit to 20 words).*

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

3. ACCOMPLISHMENTS: *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

What were the major goals of the project? *List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.*

- **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-This trial has accrued 60 patients. 99% completed.
    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.
    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. 99% completed.

b. **Subtask 2**: Circulating tumor cell (CTC) analysis: Ongoing with research collaborator. 50% 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-Ongoing.

b. **Subtask 2**: Prepare manuscript(s) for publication with mentor-Data collection and analysis is ongoing. Manuscript will be in preparation for Winter 2021.

- **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. 50% completed.

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 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? *For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.*

1) *Major activities;* In this reporting period, we accrued additional clinical trial patients with advanced prostate cancer to this project. We continued genomic analyses on metastatic sites of disease and clinical data analyses with submission of data to ASCO GU 2021 with acceptance as a poster presentation. We also published the following in May 2021:

   Chau V, Madan RA, Bilusic M, Owens H, Cordes LM, Marte JL, Gulley JL, Lee JM, Dahut WL, Karzai F. Anaplastic Features in Advanced Prostate Cancer With and Without DNA Damage Repair Mutations. Clin Genitourin Cancer. 2021 May 17:S1558-7673(21)00100-2. doi: 10.1016/j.clgc.2021.05.005. PMID: 34116956.

2) Specific Objectives; We investigated the relationship between anaplastic prostate and DNA damage repair (DDR) mutations in the patients on this trial.

3) *Significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative)*

Anaplastic prostate cancer has a poor prognosis with limited treatment options. Seven clinical features of anaplastic prostate cancer have been prospectively identified. In this phase II clinical trial, we identified mutations, including DNA damage repair (DDR) mutations, in patients with metastatic castration-resistant prostate cancer (mCRPC) who were treated with durvalumab and olaparib and determined how many of them can be described as anaplastic, and we examined the overlap between anaplastic features and DDR mutations

Patients with and without anaplastic features appear to have similar total rates of DDR mutations and also similar rates of somatic and germline DDR mutations. Patients with anaplastic features have a trend toward improved PFS when treated with olaparib and durvalumab compared with nonanaplastic patients.

Baseline characteristics were similar between anaplastic and nonanaplastic patients. Eleven patients (20%) displayed clear anaplastic features, and 43 (78.2%) lacked anaplastic features. In the anaplastic group, 2/11 (18.2%) had germline DRR mutations, and 4/11 (36.3%) had somatic DDR mutations. In the nonanaplastic group, 7/43 (16.3%) had germline mutations, and 13/43 (30.2%) had somatic mutations. Median progression-free survival (PFS) times in patients with anaplastic features (6.5 months) and without anaplastic features (5.1 months) were similar (hazard ratio 0.998, P = .996).

4) Other Achievements: Manuscript in preparation for the 60 patients accrued on this trial and publication of correlative studies described.

What opportunities for training and professional development did the project provide?
How were the results disseminated to communities of interest? *If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."*

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

This project afforded me the opportunity to be a PI on a study and develop skills as a clinical investigator. I am responsible for the regulatory and clinical oversight for the patients with mCRPC treated with durvalumab and olaparib and have gained greater proficiency. I have also had one-to-one training with my mentor, Dr. James Gulley.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Nothing to Report.

What do you plan to do during the next reporting period to accomplish the goals and objectives? *If this is the final report, state "Nothing to Report."*

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

During the next reporting period, I plan to complete the clinical analyses (including PFS and OS) for the 60 patients and compare those based on mutational status (germline vs. somatic) versus patients with no mutations found. Correlative studies, including CTC analyses, will be completed, as will the first draft of a manuscript.

4. IMPACT: D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project? *If there is nothing significant to report during this reporting period, state "Nothing to Report."*

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

This study demonstrates for the activity for the combination of durvalumab plus olaparib in prostate cancer patients with deep responses in patients with known mutations. The future of treatment for mCRPC may take us beyond androgen suppression to combination therapies such as PARP inhibition plus immunotherapy in patients with DDR mutations.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to Report.

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Nothing to Report.

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to Report.

5. CHANGES/PROBLEMS:

The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Nothing to Report.

Changes in approach and reasons for change
Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Nothing to Report

Actual or anticipated problems or delays and actions or plans to resolve them:
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

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.

Changes that had a significant impact on expenditures
Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Expenditures fell dramatically secondary to cessation of clinical trial accrual and correlative research secondary to the COVID-19 pandemic.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents:
Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

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:

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
Report only the major publication(s) resulting from the work under this award.

Journal publications: *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Chau V, Madan RA, Bilusic M, Owens H, Cordes LM, Marte JL, Gulley JL, Lee JM, Dahut WL, Karzai F. Anaplastic Features in Advanced Prostate Cancer With and Without DNA Damage Repair Mutations. Clin Genitourin Cancer. 2021, May 17:S1558-7673(21)00100-2. Published. Yes.

Books or other non-periodical, one-time publications:
Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).

Nothing to Report.

Other publications, conference papers, and presentations:
Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.

*****Vincent Chau, Ravi Amrit Madan, Marijo Bilusic, Lisa M. Cordes, Jennifer L. Marte, Helen Owens, Amy Hankin, James L. Gulley, Jung-Min Lee, William L. Dahut, Fatima Karzai. Anaplastic features (AnaF) and DNA-damage repair pathway (DDR) mutations in metastatic castration-resistant prostate cancer (mCRPC). 2021 Genitourinary Cancers Symposium. February 2021. J Clin Oncol 39, 2021 (suppl 6; abstr 92).

Website(s) or other Internet site(s):
List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to Report.

Technologies or techniques:
Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

Nothing to Report.

Inventions, patent applications, and/or licenses:
Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to Report.

Other Products:
Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

- *data or databases;*
- *physical collections;*
- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*

- *new business creation; and*
- *other.*

Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS:

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

No Change.

Name:	William L. Dahut, M.D., No change
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:	CRADA between NCI and Astra Zeneca

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:	CRADA between NCI and Astra Zeneca

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?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nothing to Report.

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Nothing to Report.

8. SPECIAL REPORTING REQUIREMENTS

QUAD CHARTS: *If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.*

9. APPENDICES:

Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.