AWARD NUMBER: W81XWH-21-1-0604

TITLE: Novel Synergistic ATR Inhibitor Combinations for Ovarian Cancer Therapy

PRINCIPAL INVESTIGATOR: Panagiotis A. Konstantinopoulos, MD, PhD

CONTRACTING ORGANIZATION: Dana-Farber Cancer Institute, Boston, MA

REPORT DATE: August 2023

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

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5b. GRANT NUMBER
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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)

Dana-Farber Cancer Institute
450 Brookline Avenue,
Boston, MA 02215-5450

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

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12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Large scale genomic studies have demonstrated that high grade serous ovarian cancers (HGSOCs) exhibit increased replication stress due to near universal loss of the G1/S checkpoint, premature S phase entry, oncogenic driver activation and deficiency in homologous recombination repair. In this application we address the potential of targeting the replication stress (RS) and the replication stress response (which is facilitated by the ATR kinase) in ovarian cancer and have proposed a set of experiments to facilitate preclinical development of novel synergistic ATRi combinations in this disease. In the Aims 1 and 2 of this award we have proposed to perform in vitro and in vivo studies to evaluate the therapeutic efficacy of ATRi in combination with CDK5, PI3K and EZH2 inhibitors in HGSOC lines, organoid models and PDX models. In Aim 3, we have proposed to evaluate the therapeutic efficacy of ATRi in combination with immune checkpoint inhibitors in genetically engineered mouse models (GEMMs) and in Aim 4 we propose to define and validate a RS biomarker of response to ATRi in tumors from patients with platinum resistant HGSOC treated on a randomized trial of gemcitabine vs. gemcitabine combined with ATRi berzosertib. In the second year of the award, we have been doing preclinical work on combinations of ATRi with PI3Ki and CDK5i inhibitors and we have been able to define novel biomarkers (such as ATM expression by immunohistochemistry) that correlates response to gemcitabine versus combined gemcitabine and ATR inhibitor therapy in HGSOC ovarian cancer.

15. SUBJECT TERMS Epithelial Ovarian Cancer, Replication stress, ATR inhibitors, Gemcitabine, PI3K inhibitors, CDK5 inhibitors, anti-PD-1 antibodies					
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Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

TABLE OF CONTENTS

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

Large scale genomic studies have demonstrated that high grade serous ovarian cancers (HGSOCs) exhibit increased replication stress due to near universal loss of the G1/S checkpoint, premature S phase entry, oncogenic driver activation and deficiency in homologous recombination repair. In this application we address the potential of targeting the replication stress (RS) and the replication stress response (which is facilitated by the ATR kinase) in ovarian cancer and have proposed a set of experiments to facilitate preclinical development of novel synergistic ATRi combinations in this disease. In the Aims 1 and 2 of this award we have proposed to perform in vitro and in vivo studies to evaluate the therapeutic efficacy of ATRi in combination with CDK5, PI3K and EZH2 inhibitors in HGSOC lines, organoid models and PDX models. In Aim 3, we have proposed to evaluate the therapeutic efficacy of ATRi in combination with immune checkpoint inhibitors in genetically engineered mouse models (GEMMs) and in Aim 4 we propose to define and validate a RS biomarker of response to ATRi in tumors from patients with platinum resistant HGSOC treated on a randomized trial of gemcitabine vs. gemcitabine combined with ATRi berzosertib.

2. **KEYWORDS:** *Provide a brief list of keywords (limit to 20 words).*

Epithelial Ovarian Cancer, Replication stress, ATR inhibitors, Gemcitabine, PI3K inhibitors, CDK5 inhibitors, anti-PD-1 antibodies

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.

Throughout the timeline of the award the following goals have been proposed:
Specific Aim 1: To perform in vitro studies of targeted inhibition of our high-confidence 'hits' from PRISM and CRISPR, alone and in combination with ATRi, in HGSOC lines and organoid models to extend mechanism-of-action studies and inform on potential combination strategies.
Specific Aim 2: To evaluate the therapeutic efficacy of ATRi in combination with CDK5, PI3K and EZH2 inhibitors in HGSOC PDX models.
Specific Aim 3: To evaluate the therapeutic efficacy of ATRi in combination with immune checkpoint inhibitors in HGSOC GEMMs.
Specific Aim 4: To define a biomarker of response to ATRi in tumors from patients with platinum-resistant HGSOC treated on a randomized trial of gemcitabine vs. gemcitabine combined with ATRi berzosertib.

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.

Prioritizing our high confidence "hits" we were particularly interested in actionable targets for which inhibitors already exist, therefore can be improved to clinical-grade, to use with ATR inhibitors in novel combinatorial strategies. These included: (i) CDK5 (ii) the epigenetic regulator EZH2; and iii) genes that were members or indirectly affected the PI3K signaling pathway. CDK5

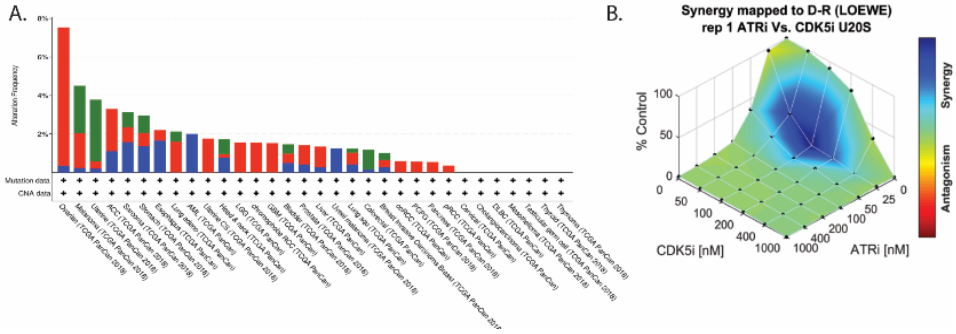

Figure 1: A) Analysis of TCGA showing that CDK5 is amplified specifically in HGSOCs. B) Combifit analysis of CDK5i and ATRi reveals significant synergy in viability assays.

was further prioritized as it is amplified specifically in HGSOC, more than other tumor types (Fig. 1).

CCNE1 (Cyclin E) amplification has been identified as a primary oncogenic driver in a subset of HGSOC and associated with genomic instability and refractory to platinum therapy. Furthermore,

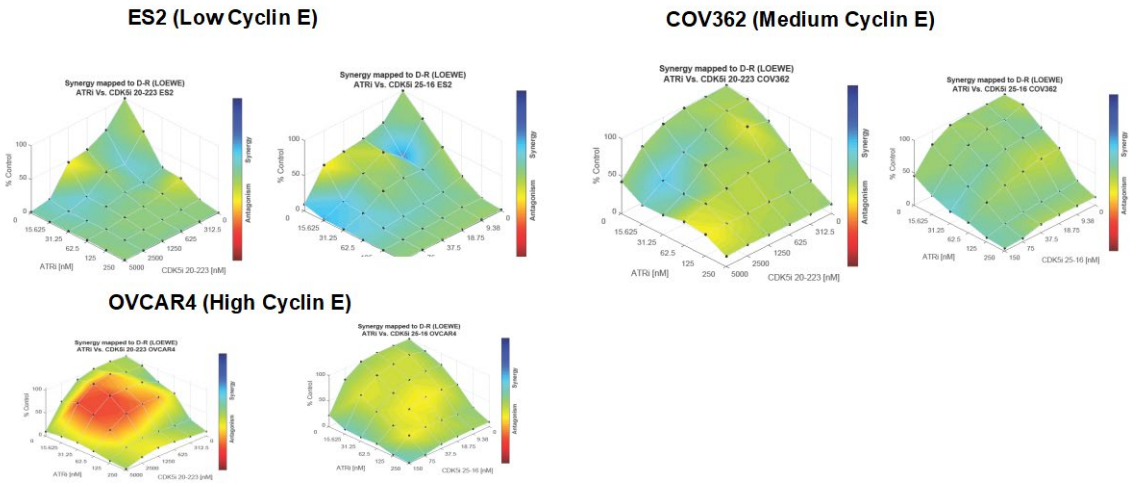

Figure 2: Combifit analysis of CDK5 inhibitor 20-223 or CDK5 inhibitor 25-16 and ATRi was conducted in indicated HGSOC lines with different levels of CCNE1 as indicated. Our analysis reveals significant synergy in viability assays only in CCNE1 low cells.

CCNE1 amplification is an established marker of replication stress (RS). Recent pre-clinical data demonstrated better ATRi responsiveness in CCNE1 amplified tumors because of the high RS background. In ovarian cancer, CCNE1 amplification is detected in about 20% of tumors, in a manner largely mutually exclusive with CDK5 amplification (data not shown). We used two independent CDK5 inhibitors (20-223 and 25-16) Interestingly, we observed synergy between ATR inhibitor BAY1895334 both the CDK5 inhibitors 20-223 and 25-16 specifically in low CCNE1-expressing HGSOC cells (Figure 2). CDK5 inhibitor 20-223 had a more significant synergistic effect with ATRi. This suggests that CDK5 inhibition and CCNE1 overexpression may be redundant in sensitizing cells to ATRi. Based on these results, we postulate that CDK5 is an actionable target that may expand the scope and efficacy of ATRi in a normal/low cyclin E expressing cancers. Also, low CCNE1 potential maybe a biomarker for CDK5 inhibitors. We further aim to elucidate the interplay between CDK5/CCNE1 in S-phase and its relevance to ATRi sensitivity. As we move onto animal studies and HGSOC organoid treatment with CDK5 inhibitors we will also focus on the other actionable targets, EZH2 and PI3-K pathway.

In the second year of the award we completed the final overall survival (OS) analysis and biomarker correlations (ATM expression by immunohistochemistry, mutational signature 3 and a genomic biomarker of replication stress) for the multicenter, open-label, randomized phase 2 trial which evaluated the addition of ATR inhibitor (ATRi) berzosertib to gemcitabine. At the data cutoff of January 27, 2023 (>30 months of additional follow-up from the primary analysis), median OS was 59.4 weeks with gemcitabine/berzosertib versus 43.0 weeks with gemcitabine alone (HR 0.79, 90% CI 0.52-1.2, one-sided log-rank p=0.18), Figure below.

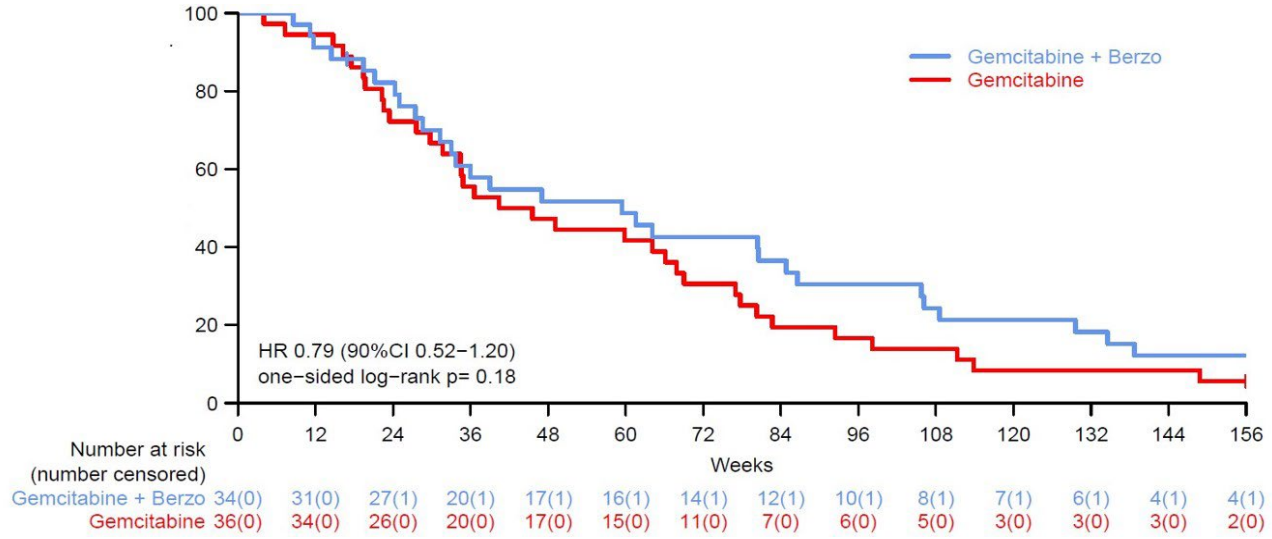

Figure. Final Overall Survival analysis (all patients)

An OS benefit with addition of berzosertib to gemcitabine was suggested in patients stratified into the platinum-free interval (PFI) ≤3 months subgroup (HR 0.48, 90% CI 0.22-1.01, one-sided log-rank p=0.04), Figure below.

Furthermore, an OS benefit with addition of berzosertib to gemcitabine was suggested in patients with ATM-negative/low tumors (HR 0.50, 90% CI 0.23-1.08, one-sided log-rank p=0.06).

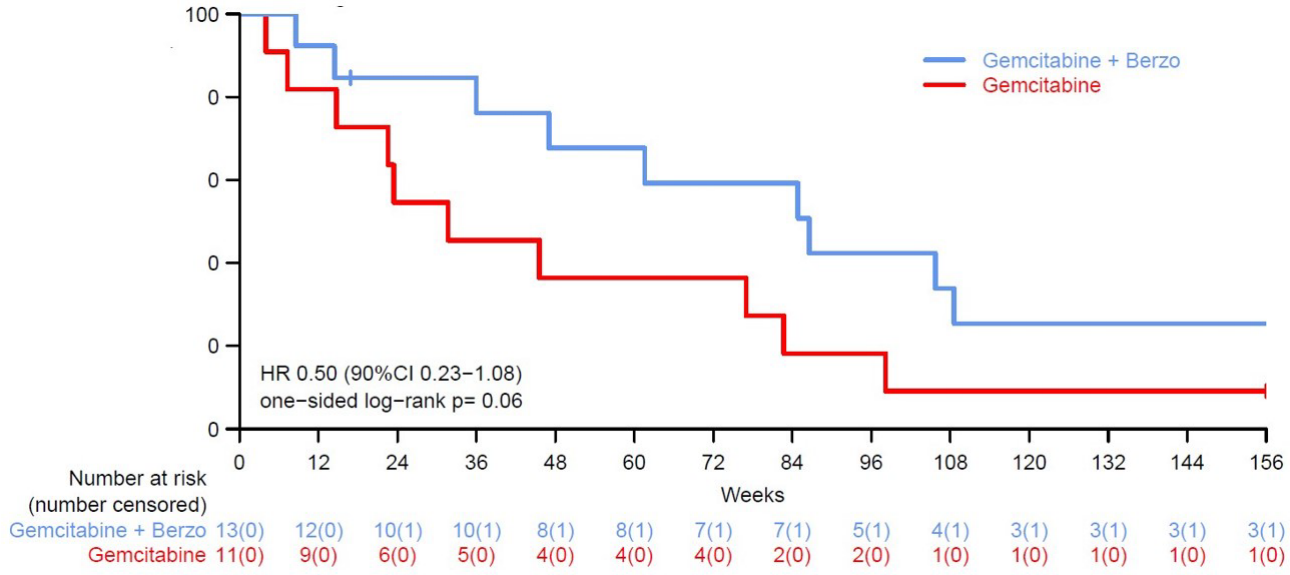

Figure. Final Overall Survival analysis (ATM negative/low by IHC)

Taken together, the results of this follow-up analysis continue to support the promise of ATR inhibitor therapy in combination with gemcitabine in platinum resistant ovarian cancer. This is a very active area of investigation with several clinical trials currently evaluating gemcitabine in combination with other ATR inhibitors including ceralasertib (NCT03669601), camonsertib (NCT04497116), elimusertib (NCT04616534) and ART0380 (NCT04657068).

These results were presented as a Poster Discussion in June 2023 at the 2023 American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago and have been submitted for publication and are currently under review.

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

"Nothing to Report."

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."

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

In the next reporting period, we aim to continue the in vitro and in vivo experiments as relevant to Aims 1, 2 and we will continue to optimize our biomarker on Aim 4.

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).

"Nothing to Report."

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."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

"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."

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.

"Nothing to Report."

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.

"Nothing to Report."

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

As recommended by the reviewers the animal work with HGSOC GEMMS will not be conducted. We plan to conduct the animal work with PDXs in Year 4 with guidance from our work with patient derived cell lines.

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).*

1. **Konstantinopoulos PA**, da Costa AABA, Gulhan D, Lee EK, Cheng SC, Hendrickson AEW, Kochupurakkal B, Kolin DL, Kohn EC, Liu JF, Stover EH, Curtis J, Tayob N, Polak M, **Chowdhury D**, Matulonis UA, Färkkilä A, D'Andrea AD, Shapiro GI. A Replication stress biomarker is associated with response to gemcitabine versus combined gemcitabine and ATR inhibitor therapy in ovarian cancer. Nat Commun. 2021 Sep 22;12(1):5574. doi: 10.1038/s41467-021-25904-w. PMID: 34552099; PMCID: PMC8458434.
2. **Konstantinopoulos PA**, Matulonis UA. Clinical and translational advances in ovarian cancer therapy. Nat Cancer. 2023 Sep;4(9):1239-1257. doi: 10.1038/s43018-023-00617-9. Epub 2023 Aug 31. PMID: 37653142.
3. Swift ML, Zhou R, Syed A, Moreau LA, Tomasik B, Tainer JA, **Konstantinopoulos PA**, D'Andrea AD, He YJ, **D Chowdhury** Dynamics of the DYNLL1-MRE11 complex regulate DNA end resection and recruitment of Shieldin to DSBs. Nat Struct Mol Biol. 2023 Oct;30(10):1456-1467.PMID: 37696958

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.*

1. Konstantinopoulos PA, Lee EK, Cheng SC, da Costa AABA, Wahner-Hendrickson AE, Gulhan D, Kochupurakkal B, Kolin DL, Kohn EC, Liu JF, Stover E, Curtis J, Sawyer H, Polak M, Chowdhury D, Färkkilä A, D'Andrea AD, Shapiro GI, Matulonis UA. Abstract #5512: Randomized phase 2 study of Gemcitabine with or without ATR inhibitor Berzosertib (M6620) in platinum-resistant ovarian cancer (OC): Final overall survival (OS) and biomarker analyses, ASCO 2023, Chicago.

"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

What individuals have worked on the project?

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".

Name: Panagiotis Konstantinopoulos
Project Role: PI
Researcher Identifier (e.g. ORCID ID): 0000-0002-1032-1479
Nearest person month worked: 1
Contribution to Project: Dr Konstantinopoulos is working on all aims on this work
Funding Support: DOD W81XWH-21-1-0604, 2P50CA240243-01Al, UMl CA186709-06, Gray Foundation Basser Initiative, 5U10CA180868, and BCRF.

Name: Dipanjan Chowdhury
Project Role: Co-PD/PI
Researcher Identifier (e.g. ORCID ID): 0000-0001-5645-3752
Nearest person month worked: 1
Contribution to Project:Dr Chowdhury is working on Aims 1-4 of this work.
Funding Support: Dr. Chowdhury is supported by the following grants: DOD W81XWH-21-1-0604, R01CA264900, The Honorable Tina Brozman Foundation for Ovarian Cancer (2), Gray

Foundation, Breakthrough Cancer Center (BTC), V Foundation for Cancer Research, U54CA274516

Name: Xiao-Feng Zheng
Project Role: Instructor
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 6
Contribution to Project: Dr Zheng is working on Aims 1 and 2 of this work.
Funding Support: Xiao is supported by this DoD grant W81XWH-21-1-0604 and 5R01CA208244-05

Name: Tahireh Markert
Project Role: Graduate Student
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 12
Contribution to Project: Tahireh has assisted Dr. Chowhdury and Zheng on their work

Name: George Lantz
Project Role: Technician
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 1
Contribution to Project: George has assisted Dr. Chowhdury and Zheng on their work

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.

Newly awarded/renewed for Dr. Konstantinopoulos

Title: Circulating microRNAs for assessment of risk beyond the BRCA genes and early detection of breast cancer in high-risk families
Goals: Our project will develop a blood test which can predict which women are most at risk for ovarian and breast cancer. Following that, we will study whether the same blood test can predict when cancer among these women is most likely to develop, increasing the chances that a cancer is found early and significantly improving the odds of survival.
AIM1: Development and validation of miRNA signatures for early detection of breast

cancers among BRCA1 and BRCA2 mutation carriers.
AIM 2: Identification and validation of circulating miRNA signatures to delineate high-risk families without known mutations.
PD/PI: Dipanjan Chowdhury
Role: Co-investigator
Dates: 9/1/23-8/31/26
Effort: 0.6 Calendar Months
Level of Funding:
Overlap: None
POC
Charlotte Baynard
Gray Foundation
595 Madison Avenue, 32nd Floor
New York, NY 10022

charlotte@grayfoundation.org

(THIS GRANT)
W81XWH211060401
The Assistant Secretary of Defense for Health Affairs endorsed by the Department of Defense
Title: Novel Synergistic ATR Inhibitor Combinations for Ovarian Cancer Therapy
Goals: Aim 1. To perform in vitro studies of targeted inhibition of our high-confidence 'hits' from PRISM and CRISPR, alone and in combination with ATRi, in HGSOC lines and organoid models to extend mechanism-of-action studies and inform on potential combination strategies. Aim 2 .To evaluate the therapeutic efficacy of ATRi in combination with CDK5, PI3K and EZH2 inhibitors in HGSOC patient derived xenograft (PDX) models. Aim 3 -To evaluate the therapeutic efficacy of ATRi in combination with immune checkpoint inhibitors in HGSOC GEMMs. Aim 4- To define and validate a RS biomarker of response to ATRi in tumors from patients with platinum-resistant HGSOC treated on a randomized trial of gemcitabine vs. gemcitabine combined with ATRi berzosertib.
Role: Principal Investigator
Dates: 8/1/21-7/31/25
Effort: 5% (0.6 CM)
Level of Funding:
POC: Stephanie Davis
Grant Specialist

Matulonis
Breast Cancer Research Foundation
Genomic relationship between ovarian and breast cancers: Predictors for chemotherapy and targeted therapy response
Goal: This study intends to explore the genetics of these two diseases with the purpose of uncovering the similarities,and studying them more carefully. The genetic alterations in common may be the most important clues to the determining the cause and treatment of the two diseases individually. 1) Generate a genomic dataset using OncoScan technology from high grade serous

ovarian cancer in patients receiving PARP inhibitors and perform genomic profiling of chromosomal alterations and mutations of common tumor suppressor and oncogenic genes to identify genomic features associated with therapy response to a PARP inhibitor. 2) Profile somatic gene mutations using whole-genome exome sequencing in cancers from aim 1 and to correlate genome-wide mutation burden and clinical response to therapy with PARP inhibitor. We will also aim to identify the mutation signature associated with outcome of therapy.
Role: Co- Investigator
Date: 10/1/2008-9/30/2024
Effort: 4.20 Calendar Months
Level of Funding:
POC:
Margaret Flowers, PhD
28 West 44th Street, Suite 609
New York, NY 10036

Fax: 646-497-0890 bcrf@bcrf.org

Recently completed for Dr. Konstantinopoulos

OCRP-OC170322
Department of Defense Ovarian Cancer Research Program
Title: Phase 1 Safety and Feasibility Study of a Personal Neoantigen-Targeting Vaccine in Combination with Immune Checkpoint Blockade in Ovarian Cancer
Goals: To conduct a study of a neoantigen targeting vaccine with PD-1 inhibition in ovarian cancer.
Role: Principal Investigator
Date: 10/1/18-9/30/21
Effort: 1.80 Calendar Months
Level of Funding:
POC:
Christopher Baker
Department of the army
US Army Medical Research Acquisition Activity
820 Chandler Street Fort Detrick MD 21702-5014

Newly awarded/renewed for Dr. Chowdhury

Title: Circulating microRNAs for assessment of risk beyond the BRCA genes and early detection of breast cancer in high-risk families
Goals: Our project will develop a blood test which can predict which women are most at risk for ovarian and breast cancer. Following that, we will study whether the same blood test can predict when cancer among these women is most likely to develop, increasing the chances that a cancer is found early and significantly improving the odds of survival.
AIM1: Development and validation of miRNA signatures for early detection of breast

cancers among BRCA1 and BRCA2 mutation carriers.
AIM 2: Identification and validation of circulating miRNA signatures to delineate high-risk families without known mutations.
PD/PI: Dipanjan Chowdhury
Role: PD/PI
Dates: 9/1/23-8/31/26
Effort: 1.2 Calendar Months
Level of Funding:
Overlap: None
POC
Charlotte Baynard
Gray Foundation
595 Madison Avenue, 32nd Floor
New York, NY 10022

charlotte@grayfoundation.org

(THIS GRANT)
W81XWH211060401
The Assistant Secretary of Defense for Health Affairs endorsed by the Department of Defense
Title: Novel Synergistic ATR Inhibitor Combinations for Ovarian Cancer Therapy
Goals: Aim 1. To perform in vitro studies of targeted inhibition of our high-confidence 'hits' from PRISM and CRISPR, alone and in combination with ATRi, in HGSOC lines and organoid models to extend mechanism-of-action studies and inform on potential combination strategies. Aim 2 .To evaluate the therapeutic efficacy of ATRi in combination with CDK5, PI3K and EZH2 inhibitors in HGSOC patient derived xenograft (PDX) models. Aim 3 -To evaluate the therapeutic efficacy of ATRi in combination with immune checkpoint inhibitors in HGSOC GEMMs. Aim 4- To define and validate a RS biomarker of response to ATRi in tumors from patients with platinum-resistant HGSOC treated on a randomized trial of gemcitabine vs. gemcitabine combined with ATRi berzosertib.
Role: CO PI
Dates: 8/1/21-7/31/25
Effort: 0.3 Calendar Months
Level of Funding:
Overlap: None
POC:
Stephanie Davis
Grant Specialist

Stephanie.p.davis12.civ.@mail.mil

Breakthrough Cancer Center (BTC)

Title: Understanding, assessing and intercepting ovarian carcinogenesis (Minimal Original Disease (MOD) Ovarian Cancer Team)
Goals: Goals: To deliver biological insight into how ovarian cancer arises, tools for its diagnosis, and surgical approaches to prevent ovarian cancer.
Aim 1. Elucidate the biology and translational implications of early ovarian cancer lesions through establishing the world's first Ovarian Precancer Atlas and corresponding computational analyses for both high-risk and average risk women. (INCLUDING THE COMPUTATIONAL BIOLOGY TEAM)
Aim 2. Engineer novel devices to rapidly image and diagnose STIC lesions in salpingectomy specimens from high-risk women.
Aim 3. Expand opportunistic salpingectomy for primary prevention in average risk women.
PD/PI: Alan D'Andrea
Role: CO PI / Lab Head
Dates: 3/1/22-2/28/25
Effort: 1.2 Calendar Months
Level of Funding:
Overlap: None
POC
Jesse Boehm, PhD
Chief Science Officer
jsb@breakthroughcancer.org

Breakthrough Cancer Center (BTC)
Title: Targeting Ovarian Cancer Minimal Residual Disease (MRD) Using Immune and DNA Repair Directed Therapies
Goals: focuses on longitudinal analyses of ovarian cancer cells and their environment.
Aim 1 We will begin with patients undergoing standard neoadjuvant therapy, interval debulking surgery, SLL, and maintenance treatment and optimize the selection of multi-dimensional analyses based on the amount and types of tissues available at various time points. Following the launch of the randomized trial of neoadjuvant chemotherapy +/- i.p. IL-12 (Subaim 2.1), optimized protocols will be applied to the precious clinical trialrelated
biospecimens. Aim 1 will also focus on developing non-invasive liquid biopsy technologies for sensitive detection of MRD and monitoring of tumor burden and response using existing specimens.
Aim 2 will leverage clinical trials and observational studies to maximize the biological understanding of MRD. The aforementioned randomized trial will test the hypothesis that inducing inflammation in the tumor environment can reduce MRD rates, while establishing an important precedent for revolutionizing testing of investigational frontline therapies using MRD rate as the primary endpoint. The second key objective of Aim 2 is to develop more efficacious and personalized maintenance and salvage therapies by incorporating knowledge of MRD and DNA damage repair vulnerabilities.
Aim 3 is closely aligned and complements Aim1 and 2 by modeling MRD in immune-competent mouse models and engaging in preclinical testing of the most promising novel therapies and targeted nanoparticle delivery modalities. This Aim is crucial for development of enabling

technologies and rational therapeutics that will iteratively by incorporated in future BTC trials for clinical testing.
PD/PI: Alan D'Andrea
Role: CO PI / Lab Head
Dates: 3/1/22-2/28/25
Effort: 0.6 Calendar Months
Level of Funding:
Overlap: None
POC:
Jesse Boehm, PhD
Breakthrough Cancer Center
jsb@breakthroughcancer.org

1R01CA264900 - 01A1
NIH
Title: Elucidating the molecular mechanism and physiological relevance of TIRR mediated inhibition of p53
Goals: : Our proposal utilizes a combination of genomic, proteomic and genetic tools to understand how TIRR inhibits p53 to promote tumor development.
PD/PI: Dipanjan Chowdhury
Dates: 7/1/2022-6/30/2027
Effort: 2.4 Calendar Months
Level of Funding:
Overlap: None
POC:
Ronald L Johnson
Program Director
NATIONAL CANCER INSTITUTE
rjohnso2@mail.nih.gov

T2022-010
V Foundation for Cancer Research
Title: Blood-based screening for identification and monitoring of women at elevated risk for breast and ovarian cancer
Goals: Aim 1. Validate models for circulating miRNA profiles for identification of BRCA1 and BRCA2 mutation carriers. Aim 2. Test models for identification of breast and ovarian cancers among BRCA1 and BRCA2 mutation carriers.
PD/PI: Dipanjan Chowdhury
Dates: 8/1/22-8/1/2025
Effort: 0.6 Calendar Months
Level of Funding:
Overlap: None
POC:
Carole C. Wegner, PhD

Senior Vice President, Research and Grants Administration
the V Foundation for Cancer Research
grants@v.org

The Honorable Tina Brozman Foundation for Ovarian Cancer
Title: Circulating microRNA signatures among BRCA1/2 mutation carriers
Goals: Aim 1. To define circulating miRNA profiles for BRCA1 and BRCA2 mutation carriers and incorporate this information into dynamic screening for ovarian cancer. Aim 2. To perform mechanistic studies exploring the effects of BRCA1 or BRCA2 mutations on miRNA expression and secretion from ovarian cancer precursor cells.
PIs: Chowdhury/Elias
Role: CO PI
Dates: 1/1/22-12/31/2023
Effort: 0.3 Calendar Months
Level of Funding:
Overlap: None
POC:
Beverly Wolfer
Executive Director

bwolfer@tinaswish.org

Recently completed for Dr. Chowdhury

2R01CA142698-10
NIH
Title: Molecular mechanism and relevance of microRNAs in DSB repair pathway choice
The major goal of this study is to investigate the impact of microRNAs on repair of DNA double strand break (DSB)s, and specifically choice of DSB repair pathways during the cell cycle.
Aim 1: Systematic identification and validation of target transcripts regulated by candidate miRNAs influencing HR- and NHEJ mediated DSB repair.Aim 2: Defining the physiological relevance of candidate miRNAs influencing HR- and NHEJ mediated DSB repair.Aim 3: To evaluate candidate miRNAs influencing HR- and NHEJ mediated DSB repair as prognostic and predictive biomarkers in epithelial ovarian cancer (EOC) and lymphomas.
Role: Principal Investigator
Date: 4/1/2015-3/31/2021*NCE
Effort: 1.92 Calendar Months
Level of Funding:
POC:
Rebecca Brightful, Grant Management Officer
RIVER 5 BG RM4083
8490 Progress Drive
Frederick, MD 21701

5R01GM129066-02

NIH
Title: Computational analysis of mutation patterns in somatic genomes
The central hypothesis of this project is that loss of DNA repair proteins representing specific pathways impacts the mutational landscape of somatic genomes providing mechanistic insights into underlying DNA damage and repair processes. Aim 1: Study epigenomic context preferences of point mutation signatures to predict etiologyAim 2: Identify tissue-level differences in mutation patterns arising from DNA repair defects.
Aim 3: Infer cell lineage-dependent patterns of mutation accumulation from the mutational landscape of terminal cells
Role: Subaward PI
Date: 4/1/2019-6/30/2021
Effort: 0.24 Calendar Months
Level of Funding:
POC:
Chrissa Papaioannous, P.E., CRA, Assistant Director of Office of Research and Sponsored Program
Rutgers, The State University of New Jersey
33 Knightsbridge Road, 1st Floor, East Wing
Piscataway, NJ 08854

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.

Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

"Nothing to Report."

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to* ***https://ers.amedd.army.mil*** *for each unique award.*

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

None.

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.*

None.