Award Number: W81XWH-18-1-0256

TITLE: Phase I/Ib trial evaluating the safety and efficacy of BET inhibitor, ZEN003694 with PD-1 inhibitor, nivolumab with or without CTLA-A inhibitor, ipilimumab in platinum resistant ovarian cancer

PRINCIPAL INVESTIGATOR: Rugang Zhang, Ph.D.

CONTRACTING ORGANIZATION: The Wistar Institute, Philadelphia, PA

REPORT DATE: October 2022

TYPE OF REPORT: Annual

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

DISTRIBUTION STATEMENT: Approved for Public Release;
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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

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1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2022	Annual	30Sep2021-29Sep2022

4. TITLE AND SUBTITLE

Phase I/Ib trial evaluating the safety and efficacy of BET inhibitor, ZEN003694 with PD-1 inhibitor, nivolumab with or without CTLA-A inhibitor, ipilimumab in platinum resistant ovarian cancer

5a. CONTRACT NUMBER
W81XWH-18-1-0256

5b. GRANT NUMBER
OC170443

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)

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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)

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

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Chemoresistance is a major cause of the high mortality of ovarian cancer. For example, although high-grade serous ovarian carcinoma (HGSOC) initially responds well to platinum-based chemotherapy, relapse often occurs with decreased chemotherapeutic sensitivity. Substantial evidence suggests that cancer stem-like cells (CSC) contribute to chemotherapy resistance. Putative epithelial ovarian cancer (EOC) CSCs are typically characterized by increased aldehyde dehydrogenase (ALDH) activity due to concomitant upregulation of the ALDH1A1 gene. It has been demonstrated preclinically that suppression of ALDH activity by ALDH1A1 knock-down sensitizes EOC cells to chemotherapy, demonstrating the functional importance of ALDH activity in EOC chemoresistance. We have furthermore shown that BRD4 (BET) inhibition reduces ALDH activity, thereby eradicating CSCs. The mechanism of suppression of ALDH activity is through downregulation of the ALDH1A1 super-enhancer associated non-coding enhancer RNA (eRNA). Notably, *BRD4* genomic locus 19p13.12 is often amplified in HGSOC (~20%), and amplification/overexpression correlates with a poor prognosis in HGSOC patients. Therefore, we hypothesize that BRD4/BET inhibition may overcome chemotherapy resistance, and plan a phase I clinical trial to evaluate the combination of BET inhibitor INCB57643 (Incyte, Inc.) with carboplatin to establish MTD, tolerability, and preliminary efficacy of the combination. We propose embedded correlative science to identify populations most likely to respond to therapy. **Our central hypothesis** is that platinum resistance can be overcome through eliminating ALDH positive cancer stem-like cells by targeting BRD4 through BET inhibition. **The goals of the proposal** are: 1) To conduct a Phase I clinical trial of combined BET inhibitor (INCB57643) and carboplatin in patients with platinum-resistant HGSOC. 2) To identify companion biomarkers that correlate with response to combination therapy in HGSOC patients.

15. SUBJECT TERMS
High-grade serous ovarian carcinoma; cancer stem-like cells; aldehyde dehydrogenase activity; super-enhancer, non-coding enhancer RNA; BRD4; Bromodomain and Extra-Terminal Motif (BET) inhibitor

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
					USAMRDC
a. REPORT	b. ABSTRACT	c. THIS PAGE	Unclassified	8	19b. TELEPHONE NUMBER *(include area code)*
Unclassified	Unclassified	Unclassified			

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1. INTRODUCTION:

Chemoresistance is a major cause of the high mortality of ovarian cancer. For example, although high-grade serous ovarian carcinoma (HGSOC) initially responds well to platinum-based chemotherapy, relapse often occurs with decreased chemotherapeutic sensitivity. Substantial evidence suggests that cancer stem-like cells (CSC) contribute to chemotherapy resistance. Putative epithelial ovarian cancer (EOC) CSCs are typically characterized by increased aldehyde dehydrogenase (ALDH) activity due to concomitant upregulation of the ALDH1A1 gene. It has been demonstrated preclinically that suppression of ALDH activity by ALDH1A1 knock-down sensitizes EOC cells to chemotherapy, demonstrating the functional importance of ALDH activity in EOC chemoresistance. We have furthermore shown that BRD4 (BET) inhibition reduces ALDH activity, thereby eradicating CSCs. The mechanism of suppression of ALDH activity is through downregulation of the ALDH1A1 super-enhancer associated non-coding enhancer RNA (eRNA). Notably, *BRD4* genomic locus 19p13.12 is often amplified in HGSOC (~20%), and amplification/overexpression correlates with a poor prognosis in HGSOC patients. Therefore, we hypothesize that BRD4/BET inhibition may overcome chemotherapy resistance, and plan a phase I clinical trial to evaluate the combination of BET inhibitor INCB57643 (Incyte, Inc.) with carboplatin to establish MTD, tolerability, and preliminary efficacy of the combination. We propose embedded correlative science to identify populations most likely to respond to therapy. Our central hypothesis is that platinum resistance can be overcome through eliminating ALDH positive cancer stem-like cells by targeting BRD4 through BET inhibition.

2. KEYWORDS:

High-grade serous ovarian carcinoma; cancer stem-like cells; aldehyde dehydrogenase activity; super-enhancer, non-coding enhancer RNA; BRD4; Bromodomain and Extra-Terminal Motif (BET) inhibitor

3. ACCOMPLISHMENTS:

What were the major goals and objectives of the project?

The major goals of the projects are:

Specific Aim 1 is to conduct a Phase I clinical trial of combined BET inhibitor (INCB57643) and carboplatin in patients with platinum-resistant HGSOC.

Specific Aim 2 is to identify companion biomarkers that correlate with response to combination therapy in HGSOC patients.

What was accomplished under these goals?

As communicated with both award specialist Ms. Kate Nagy and scientific officer Dr. Melanie Neagley, we did not start the award as initially planned due to an unforeseen issue related to the discontinuation of the experimental agent proposed in the clinical trial. In addition, the replacement trial with Dr. Kari Hacker at NYU was not started due to the fact that the latest preclinical studies no longer support the clinical trial as proposed. While we are disappointed,

we are glad that we did not start the trial as we do not want to put the patients through the trial if it does not benefit ovarian cancer patients. Consequently, we proposed to replace the trial with another clinical trial with Dr. Haider Mahdi from UPMC that aims to benefit platinum-resistant ovarian cancer patients by combining BET inhibitor ZEN-3694 with immune checkpoint blockades. The concept has since been approved by DoD OCRP. We have now all the necessary approvals to startthe award with the last no-cost-extension to 6/30/2023. We are now waiting for the contract to be approved by Ms. Kate Nagy and Dr. Melanie Neagley to finally start the trial. **As such, we do not have anything to report at this stage.**

REFERENCES N/A

What opportunities for training and professional development did the project provide?

Nothing to Report.

How were the results disseminated to communities of interest?

Nothing to Report.

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

In the final reporting period, we plan to complete the proposed replacement trail.

4. IMPACT:

Nothing to Report.

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

Nothing to Report.

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:

Nothing to Report.

Changes in approach and reasons for change

As communicated with both award specialist Ms. Kate Nagy and scientific officer Dr. Melanie Neagley, **we did not start the award as initially planned due to unforeseen issues related to the discontinuation of the experimental agent proposed in the clinical trial.**

Actual or anticipated problems or delays and actions or plans to resolve them

We have developed a replacement trial and have all the required approvals to start the trial. We will report our progress accordingly.

Changes that had a significant impact on expenditures

Nothing to Report.

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

Nothing to Report.

6. PRODUCTS:

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:	*Rugang Zhang*
Project Role:	*Principal Investigator*
Researcher Identifier (e.g. ORCID ID):	*0000-0002-7255-2360*
Nearest person month worked:	*N/A*
Contribution to Project:	*N/A*
Funding Support:	*This award*

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

The following changes occurred in the active support since the last reporting period

Deactivation of OCRA 596552 Collaborative Research Project as of 12/2021

Activation of Metabolic basis of ARID1A-mutated ovarian cancer as of 08/2022

Activation of Therapeutic Targeting Mevalonate Pathway in ARID1A-Mutated Ovarian Cancer as of 09/2022.

What other organizations were involved as partners?

Nothing to Report.

8. SPECIAL REPORTING REQUIREMENTS: None.

9. APPENDICES: None.