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TITLE: Treating Platinum Resistant Ovarian Cancer with a Combination of CD44 Blockade and PARP Inhibitor

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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

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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 and science officer Dr. Wylie, we did not start the award as initially planned due to unforeseen issue related to the discontinue of the experimental agent proposed in the clinical trial. **As such, we do not have anything to report at this stage.** However, we have since established a new collaboration with Dr. Kari Hacker at NYU for a replacement trial. The replacement trial has since been approved by the CDMRP OCRP management officers. We are waiting for the IRB approval by the NYU, which as significantly

delayed by COVID-19 related knockdown. Once the IRB protocol is approved by NYU review board, we will submit the full IRB to CDMRP officers for review and approval.

The details of the replacement trial are as below:

Primary Objective
To evaluate the safety of daily SPL-108 combined with oral talazoparib in the treatment of platinum-resistant ovarian cancer.

Secondary Objectives
To document any observed efficacy of daily SPL-108 when administered in combination with daily oral talazoparib for the treatment of platinum resistant ovarian cancer.

Study Duration
We anticipate completing the trial over a 30-month period.

Study Design
This phase I clinical trial will consist of a dose escalation phase followed by an expansion cohort. The dose escalation portion will have a standard 3 + 3 design with 3 cohorts and enroll between 9 and 18 patients. The expansion arm of this study will enroll up to 30 patients and treat them with the daily dosing of subcutaneous SPL-108 and oral talazoparib determined in the dose escalation arm for 28-day cycles.

Study Population
Eligible patients are women 18 years or older with pathologically confirmed high-grade serous ovarian, fallopian tube or primary peritoneal cancer who have completed primary treatment and have had evidence of recurrent disease less than six months following the completion of a platinum-based chemotherapy during their disease course. All patients must have current radiographic evidence of recurrent disease, a life expectancy of more than six months and an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2. They can have been treated with an unlimited number of chemotherapy regimens however cannot have received more than two previous lines of chemotherapy for platinum resistant ovarian cancer. Prior treatment with PARP inhibitors is allowed. Exclusion criteria include a diagnosis of a malignancy other than ovarian cancer within the past five years and evidence of abnormal bone marrow, kidney or liver function on laboratory tests. Patients cannot have a small bowel obstruction or active, untreated brain metastases.

Number of Participants
The dose escalation phase will enroll between 9 and 18 patients while the expansion arm will enroll between 16 and 30 patients. The total number of patients will range from 25 to 48.

Number of Study Sites
We will initially open the trial at two sites within the NYU Langone Health System, Perlmutter Cancer Center (New York, NY) and NYU Winthrop Cancer Care Center (Mineola, NY).

Translational Study Sites
Correlative translation study between expression of CD44 in tumor cells and in stromal cells with clinical response to SPL-108 will be performed at The Wistar Institute

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 next reporting period, we plan to: 1) have the full approval of the replacement trial by the CDMRP OCRF leadership; and 2) start 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

“Nothing to Report.”

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

“Nothing to Report.”

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):	*N/A*
Nearest person month worked:	
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:

Activation of "Immunological approaches for ARID1A-mutated ovarian cancer", NIH
Activation of "Regulation of tumor recurrence by stress activated neutrophils", NIH

What other organizations were involved as partners?

"Nothing to Report."

8. SPECIAL REPORTING REQUIREMENTS: None.

9. APPENDICES: None.