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TITLE: Phase 1B Trial With PTC-596 in High-Grade Serous Ovarian Cancer: a Targeted Approach Toward Chemoresistant Stem-Like Cancer Cells

PRINCIPAL INVESTIGATOR: Dr. Resham Bhattacharya

CONTRACTING ORGANIZATION:
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OKLAHOMA CITY OK 73104-3609

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Dr. Resham Bhattacharya

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8. PERFORMING ORGANIZATION REPORT NUMBER

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

This study, utilizes a second generation BMI1 inhibitor which has the potential to block development of platinum resistance among patients receiving neo-adjuvant chemotherapy (NACT). Use of NACT is only increasing and with this certainly come safer surgeries, which is a great benefit. However – early development of platinum resistance is a likely consequence as well. The ability to thwart this is being tested, via inhibition of the proto-oncogene BMI1, which results in downregulation of the multidrug resistance gene 1, which prevents cisplatin induced chemotherapy cross resistance as well as inhibits glutathione production which decreases the export of cisplatin from tumor cells. Preclinical studies in mice models have shown that inhibition of BMI1 could significantly inhibit ovarian tumor growth and combination with cisplatin could abrogate ovarian tumor growth in mice model. Therefore we have undertaken a phase 1, 3x3 dose escalation study to determine the maximum tolerated dose of the BMI1 inhibitor that can be given in combination with standard-of-care carboplatin and paclitxel. When accrual is completed efficacy in terms of pharmaco-dynamic pathway alterations will also be addressed. This combination chemotherapy has the potential to maintain the

15. SUBJECT TERMS

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Reset

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

BMI1 (B lymphoma Mo-MLV insertion region 1 homolog) is an oncogene that plays a crucial role in cancer stem-cell self-renewal and proliferation . Overexpression of BMI1 has been associated with cancer metastases, recurrence and chemo-resistance in various cancers including ovarian cancer. Targeting the proto-oncogene BMI1 is an attractive approach because it is overexpressed among patients with epithelial ovarian cancer and strongly associated with advanced stages, high-grade cancer and shorter median survival time. Preclinical studies in mice models have shown that inhibition of BMI1 could significantly inhibit ovarian tumor growth and combination with cisplatin could abrogate ovarian tumor growth in mice model. Also, silencing BMI1, significantly decreased cisplatin-mediated induction of MDR1 leading to a decreased cross-chemoresistance in ovarian cancer cells.
This study is attempting to validate these preclinical findings among women with advanced stage ovarian cancer felt to be appropriate for neoadjuvant chemotherapy. Patients will have a pre-treatment biopsy as per standard of care, some of which will be evaluated for stem cell pathways, treated with standard of care carboplatin and paclitaxel plus the BMI-1 inhibitor PTC 596 and then undergo an interval cytoreductive surgery, as per standard of care where post exposure biopsies will be obtained. This is a phase 1, 3x3 dose escalation with a planned expansion at the recommended phase 2 dose.

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

Epithelial ovarian cancer, BMI-1, maximum tolerated dose, stem cell markers, progression free survival, overall survival

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.

The major goals of this project are defined by the specific aims:
Aim 1) Determine the maximum tolerated dose (MTD) and dose limiting toxicities (DLTs) of PTC-596 in combination with and following conventional chemotherapy and as maintenance in EOC patients.

Major Task 1: Regulatory approval of IND clinical trial

Subtask 1. Regulatory approval for clinical trial

Milestone Achieved: Local IRB approval of Clinical trial and informed consent July 13, 2017

Major Task 2- Conduct phase 1b clinical trial

Subtask 1: Protocol education and training for site staff

Milestone achieved: Research staff trained Achieved August 9, 2017

Subtask 2: Enrollment and treatment of patients based on 3 + 3 dose escalation design

Milestone achieved: Study activation initiated with HRPO approval on March 15, 2019

Subtask 3: To evaluate plasma exposures of PTC596 at selected time points.

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.

Aim 1: **Major Task 1**: Regulatory approval of IND clinical trial
Subtask 1: Regulatory Approval for clinical trial
All aspects of Major and subtask 1 (inclusive of submission of the IND application to the FDA (IND 134197), Local IRB approval of the protocol and informed consent (IRB 8023), and Final protocol submission to clinicaltrials .gov (NCT03206645)) have been completed.
Major and subtask 1 categories of submitting dose limiting toxicity (DLT) reports to the Data Safety Monitoring Committee (DSMC) quarterly commenced with study activation/HRPO approval on march 15, 2019.
Similarly, submission of protocol amendments, adverse events, protocol deviations etc to the IRB and continuing IRB and PRMC review are being performed per institutional standard operating procedures.

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

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?
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.

Our site has prioritized this study for our patients who present and are appropriate for neoadjuvant chemotherapy. We intend to continue to recruit and follow the protocol to maintain patient safety, data integrity and protocol compliance. We will continue to obtain biologic specimens from consented patients and transfer these to Dr. Bhattacharya's laboratory for analysis as per the goals of this project.
Institutional standard operating procedures will be followed for data management, regulatory oversight and medical oversight.

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

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:*

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.

This 3 x 3 dose escalation design was planned conservatively due to the potential for overlapping hematologic toxicity. Patients are enrolled one at a time and followed through the DLT period (6 weeks) before enrolling another patient. Patient 1 cleared the DLT period without DLT, we have identified 2 additional patients, one who ended up having a non-ovarian cancer and were therefore excluded, and a second who consented and underwent a diagnostic procedure to confirm diagnosis but then became so ill from her cancer that she was not felt to be trial appropriate. This has led to a longer than anticipated time between patient 1 and 2. Our site will continue to screen every clinic and has confidence that this is not an ongoing problem.

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

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).*

Nothing to report

  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.*

Nothing to report

- **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

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".

Example:

Name: Mary Smith
Project Role: Graduate Student
Researcher Identifier (e.g. ORCID ID): 1234567
Nearest person month worked: 5

Contribution to Project: *Ms. Smith has performed work in the area of combined error-control and constrained coding.*

Funding Support: *The Ford Foundation (Complete only if the funding support is provided from other than this award.)*

Name: Kathleen Moore, MD
Project Role: Clinical Trial Principle Investigator
Researcher Identifier:
Nearest person month worked 2
Contribution to project: Dr. Moore wrote the clinical trial protocol including the amendment under which it opened, she screens and treats the patients who are enrolled on the clinical trial, oversees all staff involved in the protocol and is responsible for staff training, data integrity, protocol compliance and patient safety.
Name: Resham Bhattacharya, Ph.D
Project Role: Principle Investigator
Researcher Identifier: https://orcid.org/0000-0003-2523-0569
Nearest person month worked 1
Contribution to project: Overall co-ordination of the project/translational science
Name: Andrea Andrews
Project Role: Regulatory Specialist
Researcher Identifier: Not Available
Nearest person month worked 1.5
Contribution to project: Worked to assemble the IND application and respond to the FDA, register the trial on clintrials.gov and update content, worked to complete IRB and scientific review submissions.
Name: Michelle Modena RN
Project Role: Research Nurse Coordinator
Researcher Identifier: Not Available
Nearest person month worked 1
Contribution to project: Oversees coordination of research staff, infusion staff and clinic staff as it pertains to this protocol

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.

* See attached updated Other Support

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.*

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.