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TITLE: A Combination Therapy Strategy to Reverse Anti-PD-1 Therapy Resistance in Metastatic Ovarian Cancer Patients

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CONTRACTING ORGANIZATION: Georgetown University

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14. ABSTRACT
The purpose of this phase II clinical study is to investigate if administration of a vaccine (NY-ESO-179-108 peptide) before anti-PD-1 would be able to reverse the anti-PD-1 therapy resistance and increase the response in patients with platinum-resistant ovarian cancer (OC) and to correlate the presence of dysfunctional PD-1^{+}CD38^{hi} CD8^{+} T cells with the treatment outcome.
We have developed the clinical protocol based on the grant proposal submitted to DoD and prepared other regulatory documents. We have received approval of the protocol from the Clinical Research Committee (CRC), the Food and Drug Administration (FDA), the Institutional Review Board (IRB), and the USAMRDC OHARO OHRO. We have acquired support from Bristol Myers Squibb (BMS) to supply nivolumab for the trial at no cost. In addition, University of Virginia has provided the vaccine for this trial. The trial is registered with ClinicalTrials.gov and is now open. We expect to recruit the first patient in the next couple of months.

15. SUBJECT TERMS
Vaccine, anti-PD-1, resistance, safety, PFS, biomarker, PD-1^{+}CD38^{hi} CD8^{+} T cells

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1. **Introduction:**

Recently, anti-programmed death (PD)-1 antibodies have been tested in several clinical trials for ovarian cancer (OC) patients. However, monotherapies with blocking PD-1 or its ligand, PD-L1 yield a low rate of objective responses with progression-free survival (PFS) of less than 3 months for patients with recurrent or persistent OC. We have recently identified a major mechanism for the lack of response to anti-PD-1 and resistance to anti-PD-1 that would shed light on the modest clinical outcomes observed for OC patients following PD-1 blockade. We show that in the absence of optimal priming, PD-1 blockade results in generation of dysfunctional $CD8^+$ T cells that are identified by the expression of PD-1 and CD38. These cells are non-reprogrammable $CD8^+$ T cells that fail to get activated and hence could not show effector functions and incur resistance to further immunotherapy. This therapeutic resistance to anti-PD-1 could be reversed by a proper priming strategy; i.e., simultaneous administration of tumor-specific vaccine with PD-1 blockade. **Hypotheses**: 1) Administration of a vaccine (NY-ESO-179-108 peptide) before anti-PD-1 would be able to reverse the anti-PD-1 therapy resistance and increase the response in patients with platinum-resistant OC. 2) The responding patients will have lower numbers of dysfunctional $PD\text{-}1^+CD38^{hi}$ $CD8^+$ T cells than the non-responding patients. **Specific Aims: 1)** To determine the efficacy (PFS, objective response rate (ORR), overall survival (OS), duration of response (DoR), and disease control rate (DCR)) in patients with metastatic platinum-resistant OC when treated with a vaccine before anti-PD-1 therapy. **2)** To evaluate the immune profile in tumor biopsies and peripheral blood mononuclear cells (PBMCs). **Study Design:** We will conduct a phase II study exploring the safety and efficacy of NY-ESO-1 vaccine as a priming mechanism to prevent anti-PD-1 resistance in subjects with stage III/IV platinum-resistant OC. **Impact:** This Phase II trial aims to propose a rational combination treatment of NY-ESO-1 peptide administered before anti-PD-1 therapy in platinum-resistant patients to induce an optimized immune response against the OC. In addition, we expect to identify the immune-related biomarkers of resistance/response to this combination therapy that would be pivotal in developing novel treatment strategies for patients with OC.

2. **Keywords:** Vaccine, anti-PD-1, resistance, safety, PFS, biomarker, $PD\text{-}1^+CD38^{hi}$ $CD8^+$ T cells.

3. **Accomplishments:**

- **What were the major goals of the project?**

Major Goals: 1. To determine the efficacy in patients with metastatic platinum-resistant OC when treated with a NY-ESO-1 peptide before anti-PD-1 therapy. 2. To evaluate the immune profile in tumor biopsies and PBMCs.

- **What was accomplished under these goals?**

Major activities: 1. Development of the clinical protocol based on the grant proposal submitted to DoD.
2. Preparation of the Informed Consent Form (ICF).
3. Preparation of the Disease Group Cover Letter (DGCL).
4. Endorsement of support from the BMS to supply nivolumab for the trial at no cost.
5. Confidentiality disclosure agreement (CDA) and material transfer agreement (MTA) with University of Virginia was executed and vaccine is received.
6. The protocol is approved by the CRC.
7. The study is approved by the FDA.
8. The study is approved by the IRB.
9. The study is approved by the USAMRDC OHARO OHRO.
10. Protocol Calendar in OnCore and institutional sign off is finalized.
11. The trial is registered with ClinicalTrials.gov
12. The trial is now open and we have started pre-screening for patient recruitment.

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

"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?**

We will begin the recruitment of patients at the GUMC site and complete the subaward contract with the HMH so that this site can also open the trial.

4. **Impact:**

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:**

- **Changes in approach and reasons for change:** No changes.
- **Actual or anticipated problems or delays and actions or plans to resolve them:** Due to the pandemic, there were significant delays in getting the regulatory approval for the protocol. However, the protocol is now approved by the IRB and is open. We will begin patient accrual very soon.
- **Changes that had a significant impact on expenditures:** None.
- **Significant changes in use or care of human subjects:** None.

6. **Products:**

"Nothing to Report."

7. **Participants & Other Collaborating Organizations:**

What individuals have worked on the project?

Name:	*Samir N Khleif*
Project Role:	*PI*
Researcher Identifier (e.g. ORCID ID):	0000-0003-2707-5224
Nearest person month worked:	
Contribution to Project:	*As a PI, he was involved in development of the protocol for the clinical trial.*
Funding Support:	

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
No

What other organizations were involved as partners?

◊ **Organization Name:** Hackensack University Medical Center
◊ **Location of Organization:** Hackensack, New Jersey
◊ **Partner's contribution to the projec**t
  - **Collaboration**: This is the second site where the study will be conducted.

◊ **Organization Name:** University of Virginia
◊ **Location of Organization:** Charlottesville, VA
◊ **Partner's contribution to the projec**t
  - **Other:** They have provided an NY-ESO-1 peptide (residues 79-108) that they have used for their Mel60 clinical trial (NCT02126579, LPV7/tet plus TLR agonists and/or IFA).

◊ **Organization Name:** Bristol Myers Squibb
◊ **Location of Organization:** New York, NY
◊ **Partner's contribution to the projec**t
  - **In-kind support**: They will provide Nivolumab for the trial at no cost.

8. **Special Reporting Requirements:** None for this period.

9. **Appendices:** None.