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TITLE: EMT Targeting Vaccination, Concurrent with Chemoimmunotherapy, in Advanced NSCLC

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CONTRACTING ORGANIZATION: University of Washington, Seattle, WA

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Immunotherapy is a significant treatment advance for non-small cell lung cancer (NSCLC) and the only therapy that can lead to long term survival, although this occurs in less than 20% of patients. Patients receiving chemo-immunotherapy vs chemotherapy alone demonstrated a significantly longer survival. Despite this improvement, the majority of patients die within 2 years of diagnosis. High levels of tumor infiltrating lymphocytes (TIL) predict response to immune checkpoint inhibitor (ICI) therapy in animal models and lung cancer patients. Unfortunately, high levels of TIL are found in less than 10% of patients and a quarter of NSCLC patients have no evidence of TIL. Presence of CD8+ TIL is an independent prognostic variable in NSCLC and is associated with improved clinical outcomes. Strategies, such as vaccines, to increase CD8+ TIL could synergize ICI and improve survival in all NSCLC patients with advanced disease. Vaccines are able to induce tumor specific immunity and increase CD8 TIL in animal models.

Using novel techniques, we have developed STEMVAC, a multi-antigen vaccine targeting proteins in the epithelial to mesenchymal transition (EMT) pathway. EMT is the process by which anchorage dependent cancer cells develop the capacity to metastasize. We have identified upregulated proteins on the EMT pathway that are immunogenic and have defined in these proteins Type I CD4+ Th1 selective epitopes. CD4 Th1 immunity supports the generation of CD8+ cytotoxic T-cells. In animal models, STEMVAC profoundly inhibits cancer growth and results in the elimination of cells expressing EMT proteins. A Phase I trial has shown STEMVAC to be safe and immunogenic, generating high levels of peripheral blood antigen specific T-cells; similar to the levels reported with mutation-based vaccines suggesting Th1 selective epitopes act as neo-antigens.

Objective/Hypothesis. We hypothesize immunizing patients with advanced NSCLC, with measurable disease on maintenance immune checkpoint inhibitors (ICI), will generate tumor trafficking Type I T-cells resulting in increased activated CD8+ TIL. Vaccine induced TIL could "jump start" the immune system to stimulate further clinical responses with concurrent pemetrexed/pembrolizumab and eliminate lung cancer cells which have undergone epithelial to mesenchymal transition (EMT).

Specific Aims. (1) Determine whether intradermal (ID) STEMVAC+GM-CSF vaccination increases the percentage of CD8+ TIL in patients with advanced NSCLC compared to patients who receive ID GM-CSF alone, (2) Evaluate safety and potential clinical efficacy of STEMVAC immunization and concurrent pemetrexed/pembrolizumab maintenance therapy in patients with advanced NSCLC, and (3) Determine whether vaccine induced T-cells traffic to tumor and can eliminate cancer cells which have undergone EMT.

15. SUBJECT TERMS

Non-small cell lung cancer, NSCLC, STEMVAC, cancer vaccines

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1. **INTRODUCTION:**

Immunotherapy with immune checkpoint inhibitors (ICI) is a significant treatment advance for non-small cell lung cancer (NSCLC) and the only therapy that can lead to long term survival, although this occurs in less than 20% of patients. Despite this improvement, the majority of patients die within 2 years of diagnosis. Our challenge is to make immunotherapy work for all patients with lung cancer. Once T-cells are appropriately activated, the cells will home to any site of disease, migrate from the blood stream into the tissue, and kill the cancer cells until none remain. Furthermore, if "memory" is generated tumor specific T-cells will remain in a resting state able to re-expand if the cancer returns. ICI therapy is most effective in patients who have started their own immune response before treatment. Studies have found that patients with higher levels of CD8+ T-cells in their tumors (TIL) prior to treatment respond the best to ICI. Unfortunately, most patients with NSCLC have minimum levels of TIL. Our objective, in this randomized Phase II clinical trial is to evaluate whether a multiple antigen vaccine, STEMVAC, given with GM-CSF as an adjuvant, and used to immunize NSCLC patients who are not responding to immuno-chemotherapy, increases the level of CD8 T-cells in the tumor. STEMVAC might "jump start" the immune system and lead to more clinical responses.

We aim to give STEMVAC to patients with metastatic NSCLC who have gone through immuno-chemotherapy and still have measurable disease. While the patients are on a maintenance therapy with a drug called pemetrexed and an ICI called pembrolizumab, we will vaccinate patients with STEMVAC and the immune stimulator GM-CSF or with GM-CSF alone as control group. GM-CSF has been shown to have anti-tumor effects so it is important to have two arms to the study to determine which effects are due to STEMVAC and which are due to GM-CSF. Our study is designed to evaluate whether the vaccine increases CD8+ T-cells in the tumor, is safe to use in combination with maintenance immune-chemotherapy, and will result in further clinical responses. We will also test whether vaccine induced T-cells home to the tumor and eliminate cells that have undergone epithelial to mesenchymal transition (EMT), which is a process involved in metastasis.

2. **KEYWORDS:**

Non-Small Cell Lung Cancer; NSCLC; STEMVAC; Vaccine; Cancer Vaccine; Pembrolizumab; Pemetrexed

3. **ACCOMPLISHMENTS:**

What were the major goals of the project?

Specific Aims. (1) Determine whether intradermal (ID) STEMVAC+GM-CSF vaccination increases the percentage of CD8+ TIL in patients with advanced NSCLC compared to patients who receive ID GM-CSF alone, (2) Evaluate safety and potential clinical efficacy of STEMVAC immunization and concurrent pemetrexed/pembrolizumab maintenance therapy in patients with advanced NSCLC, and (3) Determine whether vaccine induced T-cells traffic to tumor and can eliminate cancer cells which have undergone EMT

What was accomplished under these goals?

Major Task 0: Design, initiate and enroll a randomized Phase II study of ID STEMVAC administered with GM-CSF as a vaccine adjuvant vs. ID GM-CSF alone in 40 advanced stage non-squamous NSCLC patients with measurable disease receiving maintenance pemetrexed and pembrolizumab (20 patients/arm).
Subtask: Finalize protocol and obtain all required approvals

- Refine eligibility criteria, exclusion criteria, screening protocol - COMPLETED
- Finalize consent form & human subjects protocol - COMPLETED
- Coordinate with Sites for IRB protocol submission and FDA amendment to IND – IN PROGRESS.
- Scientific Review Committee approval - COMPLETED
- Institutional Biosafety Committee (IBC) approval - COMPLETED
- The FDA Amendment: passed the 30 day waiting period without comment – COMPLETED
- Milestone Achieved: Local IRB obtained at UW – COMPLETED
- Regulatory documents submitted to HRPO – COMPLETED (answers to questions submitted 5/11/22)
- University of Washington IRB review – COMPLETED
- HRPO approval for University of Washington - COMPLETED

Milestone Achieved: Protocol open to enrollment – PENDING. We are working with the University of Washington to set up our orders in our electronic medical record system. This is the last step to being able to enroll and treat patients.

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?

- Now that we have IRB and HRPO approval, we are completing the remaining steps to active this study at the University of Washington and start enrolling and treating patients.
- Once the study is able to enroll patients we are planning to present this study to local physicians who treat Non-Small-Cell Lung Cancer. Our aim is to present the study at the Seattle Cancer Care

Alliance monthly meeting in July. This is helpful to be able to identify potential patients, at a specific time in their treatment, to determine if they are eligible to participate.

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

Nothing to report. We have not made any significant changes in our approach, objectives or scope of the study that has not been reviewed by the HRPO.

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

We know that it takes time, once a study first opens, to make physicians aware of the study and pass their patients along. We are aware of this and plan to make contact with local physicians on a regular basis regarding this study.

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

Significant changes in use or care of human subjects

No changes.

Significant changes in use or care of vertebrate animals

No changes.

Significant changes in use of biohazards and/or select agents

No changes.

6. PRODUCTS:

- **Publications, conference papers, and presentations**

  Journal publications.

Nothing to Report

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:	Rafael Santana-Davila MD
Project Role:	Partner Principal Investigator
Research Identifier:	0000-0001-5051-1755
Nearest person month worked:	0.00 (effort has been contributed during this phase of protocol development, but will begin now with subject enrollment.)

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

Nothing to Report

What other organizations were involved as partners?

Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

9. APPENDICES: