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TITLE: Combination Immunotherapy for the Treatment of High-Risk HER2-Positive Breast Cancer

PRINCIPAL INVESTIGATOR: Isabelle Bedrosian, MD

CONTRACTING ORGANIZATION: The University of Texas MD Anderson Cancer Center
Houston, TX 77030-4009

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Isabelle Bedrosian, MD

E-Mail: ibedrosian@mdanderson.org

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14. ABSTRACT

The goal of the proposed research is to complete a clinical trial that evaluates the ability of the combination of trastuzumab and the HER2-derived vaccine NeuVax™ (nelipepimut-S administered with the immunoadjuvant, GM-CSF) in the adjuvant setting to prevent metastatic disease in high-risk HER2-positive breast cancer patients. Completion of the trial will allow us to test our hypothesis that combination therapy with trastuzumab plus vaccination is a therapeutic modality that has minimal toxicity and will prevent disease recurrence. During this third year of funding, we have continued to accrue patients to the clinical trial (Specific Aim 1). To date, across the 22 sites participating in this trial, 237 HLA eligible patients have signed screening consents. Of those 183 (77%) qualified for the study and 54 (23%) were considered screen failures based on HLA type. Among the qualified patients, 97 have been randomized to treatment, 4 are HLA eligible and pending randomization, and 82 who are HLA eligible did not proceed (reported values as of 25 Sept 2018). Pre-vaccine series delayed type hypersensitive response evaluations have been completed for all randomized patients. Blood samples for immunologic monitoring are being collected at the specified time points, processed, and stored for the planned analyses

15. SUBJECT TERMS

Breast cancer, HER2- positive, immunotherapy, vaccines, NeuVax™, clinical trial

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1. Introduction

Despite advances in treatment, it is estimated that approximately 20% of women diagnosed with invasive breast cancer will recur and may eventually succumb to their disease. One group at high risk for recurrence are patients with HER2-positive tumors who do not achieve a pathologic complete response (pCR) after receiving chemotherapy plus trastuzumab in the neoadjuvant setting. Novel therapeutic strategies are therefore needed for patients failing to achieve a pCR. Our group has been investigating HER2-derived peptide vaccines that elicit a HER2-specific cytotoxic T lymphocyte (CTL) response. The vaccines have been administered to patients with any degree of HER2 expression (immunohistochemistry [IHC] 1+, 2+ or 3+) in the adjuvant setting to prevent disease recurrence. The vaccines are well tolerated with minimal toxicity, and stimulate a HER2-specific immune response. Early phase clinical trials suggested clinical benefit with decreased recurrence rates in vaccinated patients compared with non-vaccinated controls. In patients with HER2-positive (= 3+ by IHC) tumors (n=50) who were vaccinated after receiving trastuzumab, there have been no recurrences in the per treatment analyses after greater than 36 month follow-up. Based on these encouraging preliminary data where combination therapy virtually eliminated recurrences, we have designed and are currently conducting an adequately powered clinical trial randomizing patients that fail to achieve a pCR to receive maintenance trastuzumab alone (standard practice) or trastuzumab plus vaccine in the adjuvant setting. The primary *objective* of the trial is to assess the ability of the combination of trastuzumab and the HER2-derived peptide vaccine nelipepimut-S+GM-CSF (NeuVax) given in the adjuvant setting to prevent recurrences in patients with HER2-positive breast cancer who were administered neoadjuvant chemotherapy plus trastuzumab and failed to achieve a pCR. Completion of the trial will allow us to test our *central hypothesis* that combination therapy with trastuzumab plus vaccination is a non-toxic therapeutic modality that will prevent disease recurrence in these patients thereby eliminating the mortality associated with HER2-positive metastatic breast cancer.

2. Keywords

Breast cancer
HER2-positive
Immunotherapy
Vaccine
NeuVax™
Clinical trial

3. Accomplishments

The focus of this research is to assess the ability of the combination of trastuzumab and the HER2-derived peptide vaccine, NeuVax, given in the adjuvant setting, to prevent disease recurrence in patients with HER2-positive breast cancer who were administered neoadjuvant chemotherapy plus trastuzumab and did not achieve a pCR. To address this question, we are conducting an investigator-initiated, multi-center, prospective, randomized, blinded, placebo-controlled phase II trial allows us to test our *central hypothesis* that combination therapy with trastuzumab plus NeuVax™ (nelipepimut-S+GM-CSF) vaccination is a therapeutic modality with minimal toxicity that will prevent disease recurrence, which will eliminate HER2-positive metastatic breast cancer mortality.

Major goals

Specific Aim #1. Determine the efficacy of nelipepimut-S+GM-CSF administered with trastuzumab in the adjuvant setting in patients with HER2-positive breast cancer not achieving a pCR after neoadjuvant chemotherapy plus trastuzumab.

To address this aim, we are conducting a clinical trial entitled "Phase II trial of combination immunotherapy with nelipepimut-S + GM-CSF (NeuVax™) and trastuzumab in high-risk HER2+ breast cancer patients".

Administrative/Regulatory

- The University of Texas MD Anderson Cancer Center (MD Anderson) Institutional Review Board (IRB) Approval (proposed date of completion was pre-award)
    - Initial IRB approval obtained on 18 Jun 2014
    - Following USAMRMC ORP HRPO review, IRB approval of revised protocol was obtained on 5 Nov 2014.

- USAMRMC ORP HRPO Approval (proposed date of completion was pre-award)
    - Protocol was submitted for review on 4 Aug 2014
    - USAMRMC ORP HRPO review identified several revisions that focused primarily on identification of an independent research monitor as well as inclusion of language to indicate that USAMRMC ORP HRPO should be notified in cases of serious adverse events, can perform site visits, and have access to study-related records. These revisions were made and the protocol was re-submitted to USAMRMC ORP HRPO on 20 Sep 2014.
    - Revisions were accepted after which the protocol was re-submitted to the MD Anderson IRB where it was approved on 5 Nov 2014. Notification of that approval was forwarded to the USAMRMC ORP HRPO which ultimately approved the protocol on 29 Dec 2014.

- Trial activation (proposed date of activation was 1 Oct 2014)
    - The trial was activated on 29 Jan 2015

- Site selection (proposed date of completion was pre-award, 30 Sep 2014)
    - Screening for accrual is ongoing at 22 study sites, all of which have received IRB approval and completed site initiation visits.

- Trial amendments:
    - First amendment was approved by the MD Anderson IRB on 1 Dec 2015
        - Protocol changes include:
            - Broadened the window of time during which the vaccine could be administered after completion of trastuzumab infusion from 30-120 minutes to 15-120 minutes.
            - Added text to clarify the timing of when booster inoculations are administered.
            - Due to additional reports of the safety of peptide vaccines, the period of time during which patients are monitored following inoculation was changed from 60 minutes to 30 minutes with vital signs taken as clinically indicated.
            - Clarified the exclusion criteria related to autoimmune disease to reflect that patients with a history of autoimmune disease that are no longer requiring treatment are eligible. Specifically, changed test from "History of autoimmune disease" to "Any active autoimmune disease requiring treatment, with the exception of vitiligo."
            - Modified the instructions regarding dosage and preparation to be consistent with the new mixing instructions and Investigator's brochure for the vaccine provided by the manufacturer, Galena Biopharma.
            - Clarified how the injection site reaction is assessed depending on whether the patient returns to the study site or is contacted by phone by study staff 48-72 hours after inoculation.
            - Clarified that patients experiencing a serious adverse event (SAE) unrelated to study drug can be continued on the study if they desire to do so and it is determined safe for them to do so by the PI and the DoD study monitor. Note: There have been no issues related to this, the language was changed to provide clarity since an amendment was being submitted to address other necessary changes.
    - Second amendment was approved by the MD Anderson IRB on 11 Jul 2016.
        - Protocol changes include:

- Revised the eligibility criteria to include patients who are found to be HLA-A24 or HLA-A26 positive.
- Clarified the timing of initiation of study intervention. Specifically, revised to read "The first vaccination will be given with the third dose of maintenance Trastuzumab administered as monotherapy optimally, but may be given with later maintenance doses of Trastuzumab, provided there are at least six remaining doses of Trastuzumab to overlap with the Primary Vaccine Series (PVS)."
- Clarified that standard of care pertuzumab is allowed.
- Clarified that the area of inoculation will be at a location midway between the inguinal ligament and the knee preferably, but may be given in the arm.
- Corrected referenced appendix for the NCI CTCAE version 4.03 from Appendix B to Appendix C.
- In section 4.4.4 detailing blood collection and processing, clarified the immunologic assessments to be consistent with the study flowchart.
- Added to the protocol a formal interim analysis for safety to be performed after the midpoint of enrollment and randomization.

  - Third amendment was approved by the MD Anderson IRB on 14 May 2017.
    - Protocol changes include:
      - Clarification that the vaccine could be administered 15-120 minutes after completion of trastuzumab infusion. Previously the protocol stated 30-120 minutes, but 15 minutes after PI approval.
      - Clarified that the period of observation after inoculation would be 30 min +/- 5 minutes. Previously stated 1 hour.
      - Clarified that the history and physical examination as well as height and weight assessment could be performed by an advance practice practitioner designated by the physician.

- The Study Chair of the protocol was changed from Dr. Elizabeth Mittendorf to Dr. Isabelle Bedrosian on November 13, 2017. This change was made when as Dr. Mittendorf has moved from MD Anderson to the Dana-Farber/Brigham and Women's Cancer Center

<u>Trial accrual</u>

We anticipated that trial accrual would take 2 years to complete (Oct 2014 – Oct 2016). Enrollment of patients with HER2-positive breast cancer began late January 2015. As of 25 Sept 2018, 237 patients (HLA-typed) signed screening consent forms. Of these, 183 patients have qualified to continue on the study, based on HLA-A2/A3/A24/A26 status. Ninety-seven patients have been randomized to treatment and are currently on treatment, 4 patients are HLA+ and are pending randomization, and 82 patients are HLA+ but did not proceed with the trial.

No unexpected or grade > 2 adverse events were reported. The majority of patients experienced expected/related low grade (grade 1 or 2) local toxicity, including pruritis and erythema at the injection site.

<u>Specific Aim #2</u>. *Evaluate immunologic responses to nelipepimut-S+GM-CSF administered with trastuzumab.*

- *In vivo* immune responses are being determined using a delayed type hypersensitivity (DTH) response performed pre-vaccination, one month after completion of the primary vaccination series and 6 months ± 2 weeks after the fourth booster inoculation. To date, pre-vaccination DTH has been completed for all randomized patients.

- *In vitro* immune responses will be assessed using a dextramer assay on peripheral blood mononuclear cells, collected at multiple time points including pre-vaccination (R0), after completion of the primary vaccination series (PVS) (R6), prior to the first booster inoculation (RC6/B1), 1 month ± 1 week after the first booster inoculation (RB1) and 6 months ± 2 weeks following the final booster. To date, blood samples have been sent to a research lab at MD Anderson, where they have been processed and stored. Samples

are being batched so that dextramer analyses at specific time points will be completed for all patients at the same time.

Specific aim #3. Obtain well annotated blood specimens from patients treated with trastuzumab + nelipepimut-S+GM-CSF or trastuzumab + GM-CSF alone to perform correlative studies.

- Blood samples are being drawn at designated time points. Specimens have been sent to a research lab at MD Anderson, where they have been processed and stored for use in performing correlative studies.

Opportunities for training and professional development

Nothing to report,

Dissemination of results to communities of interest

Nothing to report

Plans during next reporting period to accomplish goals

To encourage trial accrual, a monthly teleconference to communicate with investigators at all of the enrolling sites was instituted. These teleconferences continue. In addition, the PI will continue to communicate with colleagues in medical and surgical oncology regarding the trial. The Research Nurse will continue to approach patients earlier in their care (during their neoadjuvant treatment, or at their pre-operative visit) to advise them of the availability of the trial. As patients enroll on the study and move through their primary vaccination series and into their booster inoculations, we will continue to complete *in vivo* immune monitoring using the DTH reaction, as well as to draw blood for *ex vivo* immune monitoring and other correlative studies.

4. Impact

Impact on the development of the principal discipline(s) of the project

Nothing to report

Impact on other disciplines

Nothing to report

Impact on technology transfer

Nothing to report

Impact on society beyond science and technology

Nothing to report

5. Changes/Problems

Changes in approach

Adjustments to the clinical trial protocol were made and approved by the IRB (detailed above):

- Initially, enrollment was restricted to patients with expression of HLA-A2 and HLA-A3. Nelipepimut-S was also found to bind to HLA-A24 and HLA-A26. Therefore, patients expressing these additional alleles are now eligible.
- Standard of care was adjusted to include treatment with pertuzumab.
- At the midpoint of enrollment and randomization (50^{th} patient), a formal interim analysis for safety will be performed.

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

Due to the Food and Drug Administration's approval of the drug, pertuzumab (Perjeta®) in the neoadjuvant setting for patients with HER2-positive breast cancer, pCR rates have been higher than anticipated, thereby decreasing the number of eligible patients for this study. In order to meet accrual targets within the specified 2-year period, we increased the number of participating sites to 22.

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

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

7. Participants & Other Collaborating Organizations

Name	Isabelle Bedrosian, MD
Project role	Principal Investigator
Research Identifier (e.g. ORCID ID)	ORCID ID: 0000-0002-8775-8361
Nearest person month work	1
Contribution to project	Dr. Bedrosian serves as the PI for the clinical trial
Funding support	The award supports 7.5% effort (0.9 calendar months) for Dr Bedrosian; her remaining salary is covered by other grants and the Department of Breast Surgical Oncology

Name	Elizabeth A. Mittendorf, MD, PhD
Project role	Co-Investigator
Research Identifier (e.g. ORCID ID)	emittendorf
Nearest person month work	3
Contribution to project	Dr. Mittendorf is overseeing the entire project

Funding support	A subaward on this grant is providing 2.5% effort for Dr. Mittendorf to provide project oversight.

Name	Olivia Butler, RN, MBA
Project role	Research Nurse
Nearest person month work	12
Contribution to project	Ms. Butler serves as the lead research nurse for the trial. She conducts all aspects of the study at MD Anderson and serves as a resource for research nurses at other enrolling sites.
Funding support	The current award supports 40% effort, 4.8 calendar months of salary support. The remaining salary is covered by the Department of Breast Surgical Oncology

Name	Anne Philips, PhD
Project role	Laboratory Coordinator
Nearest person month work	6
Contribution to project	Dr. Philips is overseeing the collection, processing, and storage of PBMC and serum samples. She also oversees the collection of blood for HLA testing and coordinates with the CLIA-certified human flow lab to ensure that testing is completed and results are distributed to participating sites.
Funding support	The award supports 70% effort (8.4 calendar months) for Dr. Philips. Her remaining salary is covered by the Department of Breast Surgical Oncology

Change in active other support of the PD/PI(s) or senior/key personnel since the last reporting period

Dr. Bedrosian's active support:

NIH/NCI 1U01CA189240-01 El-Zein/Bedrosian (co-PI) 04/01/2015 – 03/31/2020
Integrative molecular and imaging approaches for risk of subtype specific breast cancer
Objective: To develop an integrated imaging and blood biomarker model for prediction of subtype specific breast cancer risk.

Duncan Family Institute Bedrosian (PI) 11/1/2016 – 10/31/2018
Objective: Targeting of mIRNA-140 and its downstream pathway for prevention of triple negative breast cancer To investigate molecular changes in early breast cancer

NIH/NCI Alliance NCORP Buckner (PI) 08/01/2014 – 07/31/2019
NCI Community Oncology Research Program (NCORP) Research Base
Objective: Supports activities relevant to the role of co-chair of the Alliance Prevention Committee including: i) identify new areas of research opportunity and develop prevention related trials for the NCORP network, ii) oversight of existing trials to help meet accrual targets, iii) participate in NCI Prevention Steering Committee meetings

MD Anderson Breast Cancer Moonshots Program Bedrosian (PI) 09/01/2017 – 08/31/2018
Novel Therapeutic Strategies for High Risk HR+ Breast Cancer

Objective: To develop a portfolio of clinical trials that test novel strategies to address high residual risk of relapse in women with HR+ breast cancer who have completed standard of care therapy; ii) characterize the molecular response to treatment response and resistance; iii) test combination therapies that may enhance the efficacy of endocrine therapy

Dr. Mittendorf has had the following changes in other support:

- Grants closed

Cancer Insight, LLC Mittendorf 08/01/2013 – 07/31/2018
Combination immunotherapy with Herceptin and the HER2 vaccine E75 in low and intermediate HER2-expressing breast cancer patients to prevent recurrence.
This contract is supporting the conduct of a phase II clinical trial as well as for performing HLA testing for trial participants and collecting, processing and storing blood samples obtained from patients enrolled on the trial. This is a multi-center trial. Dr. Mittendorf is the institutional principal investigator and is overseeing the biospecimen collection portion of the study.

Cancer Insight, LLC Mittendorf 07/01/2013 – 06/30/2018
Phase Ib trial of two folate binding protein (FBP) peptide vaccines (E39 and J65) in breast and ovarian cancer patients.
This contract is supporting the conduct of a phase Ib trial evaluating two folate binding peptides; E39 which is the wild-type and J65 which is an attenuated version. This is a single site trial; Dr. Mittendorf is the principal investigator.

NIH Alliance for Clinical Trials in Oncology 7U10CA076001-13 Hunt 09/01/2012 – 08/31/2018
Alliance Z11102: Impact of breast conservation surgery on surgical outcomes and cosmesis in patients with multiple ipsilateral breast cancers.
This grant supports the conduct of a cooperative group study evaluating breast conserving surgery in patients with multifocal or multicentric breast cancer. Dr. Mittendorf serves as the institutional principal investigator.

- New active grant

Susan G. Komen SAC170080 Mittendorf (PI) 04/01/2018-03/31/2021
Characterizatoin of the Immune Microenvironment in HER2+ breast cancer to enhance response to standard therapy
The objective of this project is to is to fully characterize the immune microenvironment in tumors from HER2+ breast cancer patients before and after neoadjuvant chemotherapy + HER2-targeted therapy.

Other organizations involved as partners

- SELLAS Life Sciences
  15 W. 38th Street, 10th Floor
  New York, NY, 10018

  SELLAS Life Sciences provides the study drug and funding to Cancer Insight (Contract Research Organization; see below) for their role in the conduct of this study.

- Cancer Insight, LLC
  600 Navarro Street, Suite 500
  San Antonio, TX 78205

Cancer Insight oversees conduct of the study at sites other than MD Anderson Cancer Center. At these sites, they are responsible for site set-up, training and initiation, study drug distribution, inventory, and accountability; data collections and management through electronic data capture; site management, monitoring and auditing; and financial management through contracting and pass-through cost distribution.

8. Special Reporting Requirements

Not applicable

9. Appendices

None