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TITLE: Phase II Study of HER-2/neu Intracellular Domain Peptide-Based Vaccine Administered to Stage IV HER2 Positive Breast Cancer Patients Receiving Trastuzumab

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13. SUPPLEMENTARY NOTES

14. ABSTRACT
The primary purpose of this grant is to determine the overall survival benefit in Stage IV HER2 positive breast cancer patients vaccinated with a HER2 ICD peptide-based vaccine while receiving maintenance trastuzumab. The scope of the work includes a Phase II single arm study of a HER2 ICD peptide based vaccine given concurrently with trastuzumab. Patients enrolled will be HER2 over expressing stage IV breast cancer patients who have been treated to a clinical complete remission or have stable bone only disease and are within 6 months of starting maintenance trastuzumab. There have been no major findings to date. The vaccine has been manufactured, vialed, and tested for quality assurance. The study has been approved by both the FDA and our Human Subjects Division, and we are currently waiting for the approval of the USAMRMC HSRRB to approve this project so we may begin enrolling subjects into this study.

15. SUBJECT TERMS
Immunotherapy, Vaccine, HER2/neu, CD8, Cytotoxic T Lymphocytes

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INTRODUCTION

The subject of this grant is to determine whether a HER-2/neu (HER2) intracellular domain (ICD) peptide vaccine, administered in combination with trastuzumab, will impact outcomes in patients with Stage IV HER2-positive breast cancer. The primary purpose of this grant is to determine the overall survival benefit in Stage IV HER2 positive breast cancer patients vaccinated with a HER2 ICD peptide-based vaccine while receiving maintenance trastuzumab.

The scope of the work includes a Phase II single arm study of a HER2 ICD peptide based vaccine given concurrently with trastuzumab. Patients enrolled will be HER2 over expressing stage IV breast cancer patients who have been treated to a clinical complete remission or have stable bone only disease and are within 6 months of starting maintenance trastuzumab. The primary objective is an estimate of overall survival (OS) compared to a historical control of patients treated with chemotherapy and trastuzumab (55% at 2 years). We hypothesize that the overall survival rate at 2 years with vaccination, if successful, would be 75%. 52 patients will provide 92% power to detect a statistically significant increased survival rate compared to the fixed historical rate of 55% at the one-sided significance level of .05. Secondary objectives include the assessment of the toxicity of the combined approach as well as the immunogenicity of HER2 ICD peptide vaccination. If there is evidence to suggest that the true rate of Grade IV toxicity exceeds 5% or the true rate of Grade III-IV toxicity exceeds 10% then the trial will be stopped for safety concerns. Immunogenicity of the approach will be evaluated as the ability of the vaccine to elicit HER2 ICD specific T cell immunity, to elicit epitope spreading, and to stimulate both a CD4+ and CD8+ immune response. Immune response and epitope spreading will then be modeled as time-dependent covariates in Cox proportional hazards regression models for OS to assess the correlation of each of these outcomes with the hazard of mortality.

BODY

Task 1*: To assess the potential clinical impact of the administration of a HER2 ICD peptide-based vaccine to Stage IV breast cancer patients receiving concurrent trastuzumab monotherapy*

a. Reconstruct and vial the HER2 ICD peptide vaccine. This task has been completed. The vaccine product (lot 6002) has been monitored at specific intervals for product stability. A Stability Study Log for lot 6002 is maintained. The study log lists the testing dates and provides a summary table to record data for each time point tested. All reserved stability vials are stored under the same conditions as the final product, -20 ± 2°C. At each stability time point reserved vials are removed from storage and visually inspected for appearance. MALDI-TOF mass spectrometry and High Performance Liquid Chromatography (HPLC) are used to confirm the stability. Five sets of real-time stability data encompassing 360 days have been collected on ICD Vaccine lot 6002. Analysis of the data collected matches the expected results for appearance, identity (mass spectrometry) and purity (HPLC). Based on this real-time stability data the final storage condition for the ICD Vaccine is supported and considered to be satisfactory. Once we have obtained approval from the U.S. Army Medical Research and Materiel Command Human Subjects Research Review Board (HSRRB) we will notify the IDS Pharmacy that we are preparing to enroll subjects.

b. Enroll and treat patients. We have not enrolled any subjects into this study during the annual review period of April 27, 2005 to April 26, 2006. We are currently waiting approval from the US Army Medical Research and Materiel Command (USAMRMC) Human Subjects Research Review Board (HSRRB) before we begin our accrual to this study. Table 1 outlines our efforts, since May 2004, to get this study approved and open to accrual.

Table 1 – Tasks related to obtaining approval from USAMRMC HSRRB

	Date of Communication	**Comments**
Original Submission	May 2004	Uploaded all required documents as a PDF
USAMRMC	February 14, 2005	Attached to an email was a copy of the

	Date of Communication	Comments
		initial memorandum for record (MFR) for our project
Dr. Disis	June 14, 2005	Mailed hard copies of our response and corresponding documents with requested changes
USAMRMC	August 5, 2005	Phone call requesting we include all changes made to clinical documents since May 2004 which included both those requested by USAMRMC (submitted June 14, 2005) and our Human Subjects Division
Dr. Disis *	September 10, 2005	Emailed modified electronic files to included both the requested changes of USAMRMC and those approved by our Human Subjects Division
Dr. Disis	September 13, 2005 (received by USAMRMC to the attention of Ms. Oringer)	Mail hard copies of forms that were not available in an electronic format (IND submissions, certifications and chart forms)
Dr. Disis	September 26, 2005	Research Coordinator, Ms. Childs emailed Ms. Oringer to confirm all documentation had been received and if any further documentation was requested
USAMRMC	October 12, 2005	Requested we send the entire New Protocol IND submission with all attachments
Dr. Disis	October 17, 2005 (received date by USAMRMC to the attention of Ms. Oringer)	Mailed hard copies of the entire new protocol IND submission
Dr. Disis	October 26, 2005	Left a phone message for Ms. Oringer to confirm all required documentation had been received
Dr. Disis	November 2, 2005	Emailed Ms. Oringer to follow up the October 26, 2006 phone call confirming that all documents had been received and requested a rough timeline of events in terms of HSRRB review
Dr. Disis	December 2, 2005	Emailed Ms. Duchesneau requesting the same confirmation and rough timeline as on November 2, 2005
USAMRMC	January 5, 2006	Email from Ms. Oringer requesting that the highlighted documents, submitted by September 10, 2005 could not be accepted with tracked changes
Dr. Disis	January 5, 2006	Emailed all of the same documents without the tracked changes
USAMRMC	January 5, 2006	Ms. Oringer requested that we remove all of the sections of the documentation that contained strikethroughs

	Date of Communication	Comments
Dr. Disis	January 5, 2006	Submitted the same documents as those submitted September 10, 2005 without tracked changes and without the strikethroughs
USAMRMC	January 12, 2006	Received phone call from Ms. Oringer requesting additional information: a copy of our contact page for our website, completion dates of Human Subjects Protections certification and provide a copy of the Tumor Vaccine Group Specimen Repository
Dr. Disis	January 18, 2006	Faxed requested documentation except for GCP certification as requested on the January 12, 2006 phone call
Dr. Disis	February 23, 2006	Faxed GCP and Human Subjects Protections certifications as requested on the January 12, 2006 phone call
USAMRMC/Dr. Disis	February 8, 2006	Dr. Disis and Ms. Childs participated in a conference call with HSRRB to answer questions about the project before they conducted their review
USAMRMC	March 1, 2006	Emailed the DRAFT results from the February 8, 2006 HSRRB meeting
USAMRMC	March 22, 2006	Emailed the FINAL results from the February 8, 2006 HSRRB meeting
Dr. Disis	March 23, 2006	Emailed the response to the February 8, 2006 HSRRB review and all corresponding electronic documentation
Dr. Disis	March 24, 2006	Faxed those documents related to the February 8, 2006 HSRRB review that were not in an electronic format
Dr. Disis	March 28, 2006	Faxed the signed response letter and Dr. Coveler's CV
Dr. Disis	April 4, 2006	Faxed Dr. Livingston's updated Human Subjects Protection Certification
Dr. Disis	April 6, 2006 (received by Ms. Oringer)	Mailed a complete hard copy document with all required information (including the signed response and all of the information faxed above)
USAMRMC	May 8, 2006	Phone call from Ms. Oringer informing us that all documentation content had been updated and was ready for submission to our IRB
USAMRMC	May 8, 2006	Emailed the revised documentation for our IRB review and approval
Dr. Disis	May 9, 2006	Emailed formatting changes to Ms. Oringer that were made to the documents to the IRB as an FYI

*After the May 2004 submission date we continued to review this project and make changes that were found during routine monitoring of other active studies and were appropriate. As a result we submitted modifications to the protocol, consent and other documents to our Human Subjects Division for approval.

Although not actively recruiting for the study, during the previous year we have identified several potential subjects for this trial by evaluating them for other studies ongoing by our group. Due to the very specific eligibility criteria where subjects must be enrolled within 6 months of initiating maintenance trastuzumab we have lost these subjects to other studies or they have not been able to participate in a clinical trial at all as they continued to fall outside of the 6 month window. Table 2 provides a summary of the potential subjects that have been identified.

Table 2: Summary of potential subjects that have become ineligible during the last reporting period

Number of Patients	Initial Contact	Began Maintenance Herceptin	Must Begin Study By	Potentially Eligible
1	9/28/2005	Jun-05	Dec-05	
2	11/28/2005	Aug-05	Feb-06	
3	9/9/2005	Jan-06	Jul-06	X
4	12/7/2005	Jul-05	Jan-06	
5	7/13/2005	Oct-05	Apr-05	
6	12/8/2005	Dec-05	Jun-06	X
7	4/26/2005	Jan-05	Jul-05	
8	3/21/2005	Dec-05	Jun-06	X
9	4/21/2005	Mar-05	Sep-05	
10	7/15/2005	Jul-05	Jan-06	
11	7/11/2005	Aug-05	Feb-06	
12	4/20/2005	Oct-05	Apr-05	

We have obtained all necessary approvals for this project through our institution and the FDA. We obtained initial IRB approval March 24, 2004 and was recently renewed for another year on February 22, 2006, we have been approved to see subjects in the General Clinical Research Center as of May 12, 2005, Radiation Safety approval was last updated on March 3, 2006 and we submitted a New Protocol Application to the FDA to BB-IND 6524 on April 15, 2005 which has been provided to USAMRMC on October 17, 2006.It should be noted that as of February 22, 2006 all future reviews of this study will now be conducted by the Fred Hutchinson Cancer Research Center Cancer Consortium IRB rather than the UW of Washington Human Subjects Divisions.

c. Interim statistical analysis after 25 patients have been followed for 1 year: Not applicable for this reporting period. It is understood that once we have enrolled 25 subjects that have been followed for 1 year we should perform an interim analysis of the data.

d. Final analysis of response: Not applicable for this reporting period.

Task 2*: To evaluate the safety of administering a HER2 ICD peptide-based vaccine to Stage IV breast cancer patients receiving trastuzumab monotherapy*

a. Evaluate immediate toxicity associated with the vaccine. Not applicable to this reporting period. We will use the NCI Common Toxicity Criteria for Adverse Events Version 3.0 to grade toxicities. We will pay particular attention to local reactions associated with the injection site and systemic reactions to include but not limited to fever, malaise, myalgia, nausea and headache.

b. Determine whether there is any cardiac toxicity associated with the co-administration of the HER2 ICD peptide based vaccine with trastuzumab. Not applicable to this reporting period. When subjects are enrolled we will closely monitor and document any abnormal cardiac events observed by us at clinic visits or reported to us by the subjects or physicians.

c. Evaluate for any potential toxicities due to the generation of an immune response to HER2. Not applicable to this reporting period.

Task 3*: To determine the immunogenicity of a HER2 ICD peptide-based vaccine in patients with Stage IV breast cancer receiving concurrent trastuzumab monotherapy*

a. Determine the immunogenicity of the approach by assessing the T cell response to HER2 ICD. We have established overlapping peptide pools for the HER2 ICD and have demonstrated in sorted samples that these peptides, as antigens, are equivalent to recombinant protein. The standardization of this assay is significant as the use of peptide pools ensures reproducibility of evaluation over time and removes any potential inherent immunogenicity associated with recombinant protein use. In addition, we have completed the quality assurance on the ELISPOT assay proposed and have established positive and negative controls.

b. Determine the incidence of epitope spreading to the HER2 ICD or other peptides in the immunizing mix (intermolecular epitope spreading). Not applicable to this reporting period.

c. Determine the incidence of epitope spreading to other immunogenic proteins associated with breast cancers (extramolecular epitope spreading). Not applicable to this reporting period.

d. Assess the absolute magnitude of the CD4+ and CD8+ HER2 specific immune responses generated after active immunization. Not applicable to this reporting period.

e. Evaluate the generation of HER2 specific antibody immunity and antibody avidity. Not applicable to this reporting period.

f. Determine whether overall survival is associated with the development of HER2 specific T cell response or epitope spreading after active immunization. Not applicable to this reporting period.

KEY RESEARCH ACCOMPLISHMENTS

Not applicable to this reporting period.

REPORTABLE OUTCOMES

Not applicable to this reporting period.

CONCLUSIONS

The vaccine has been manufactured, vialed, and tested for quality assurance. The study has been approved by both the FDA and our Human Subjects Division and we are currently waiting for the approval of the USAMRMC HSRRB to approve this project so we may begin enrolling subjects in to this study.

REFERENCES

None

APPENDICES

None