A PHASE II STUDY OF 5T4-MODIFIED VACCINIA ANKARA (MVA) VACCINE (TROVAX®) IN PATIENTS WITH ADVANCED BREAST CANCER

Scientific Abstract

Background

Despite recent advances in the conventional treatment of solid tumors, patients with advanced breast cancer may relapse after definitive therapy because of residual microscopic disease. One potential approach to the eradication of residual sub-clinical disease is in the utilization of tumor vaccines that focus on generating tumor-specific T cell immunity. The primary immune response induced through active immunization may lead to the development of immunologic memory resulting in a long-lived protective immune response to prevent cancer relapse. Multiple breast cancer tumor associated antigens (TAA) have been identified and several cancer vaccine studies have now demonstrated that patients can be immunized against TAA and are able to develop tumor antigen specific immune responses post-immunization. One such tumor antigen is 5T4, an oncofetal protein that is overexpressed in more than 80% of breast tumors. Recent clinical studies have shown vaccination with 5T4 in a pox viral vector known as modified vaccinia Ankara (MVA) to be safe and effective in generating a 5T4-specific T cell and antibody immune response. Whether generation of a 5T4-specific immune response has an effect on the progression or relapse of breast cancer is not known. Thus, we propose a Phase II clinical trial to assess the effect of MVA-5T4 immunization on PFS in patients with Stage IIIB, Stage IIIC, and Stage IV (NED) breast cancer.

The human oncofetal antigen 5T4 is a 72 kDa transmembrane glycoprotein that is normally expressed at high levels in the placenta, specifically on trophoblasts and at very low levels on a restricted number of normal tissues. Expression of 5T4 is also up-regulated in many epithelial cancers and pre-malignant tissues including those of the breast, lungs, cervix, stomach, pancreas, colon, ovary, and kidney and thus, has been characterized as a TAA. 5T4 overexpression is associated with worse clinical outcome in patients with colorectal, gastric and ovarian carcinoma. In addition, overexpression of 5T4 is also associated with cancers of high metastatic potential. 5T4 is concentrated at microvillous projections of the plasma membrane and overexpression in epithelial cells is associated with changes in morphology, disruption of actin/cadherin-containing contacts, and increased motility suggesting a direct role of 5T4 in tumor metastasis.

Several factors including surface expression on over 70% of common tumors and restricted normal tissue expression have identified 5T4 as an optimal target for immunotherapeutic strategies. One such strategy is immunization with 5T4-MVA. Advantages of using an attenuated pox viral vector such as MVA include the ability to efficiently penetrate cells and mimic natural infection, thereby inducing potent cell mediated immune responses. In addition expression of tumor antigens such as 5T4 inside the cell may facilitate antigen processing and presentation associated with MHC class I molecules and result in potent CTL responses.

The TroVax dose level chosen for the study, 10X ($5x10^8$ pfu/$1x10^9$ $TCID_{50}$/ml) has been validated in a Phase I study (TV1 described in Section 3.0 of protocol). TroVax was safe and well tolerated at all doses and no serious adverse events were reported as being related to the vaccine. The schedule for this study is based on previous TroVax Phase I/II protocols (TV1). The first series of injections are referred to as the priming (prime) injections and the second series is referred to as the boosting injections. The strategy for this study will be to identify a schedule that generates an immune response and is similar to that used in TV1 and previously published Phase I/II trials using pox viruses.

Several clinical trials have demonstrated the patients with advanced stage disease including breast cancer can be immunized against specific targeted tumor antigens and thus, generate an immune response against their tumor.

In more recent vaccine studies, induction of an anti-tumor immune response has been associated with prolonged overall survival. In these studies induction of a measurable vaccine-specific DTH response, a well characterized in vivo surrogate of systemic antigen-specific immunologic memory and/or T cell responsiveness was associated with improved clinical response. Thus, it appears that vaccination offers a potential therapeutic strategy to prevent the relapse of disease by establishing an effective memory response targeting specific cancer antigens.

Evaluation of systemic 5T4-specific immunity will include both T cell and antibody analysis as described in Section 19.0 of the protocol.

Objectives

The objectives of this Phase II study are:

1. To assess the feasibility of conducting a live viral vaccine trial in the Stage IIIB, IIIC, IV (NED) breast cancer population in the cooperative group setting.

2. To estimate progression-free survival in patients with Stage IIIB, Stage IIIC or Stage IV (NED) breast cancer receiving 5T4-modified vaccine Ankara (MVA) immunization.

3. To assess 5T4-specific T-cell immune response (Th and CTL) to immunization with 5T4-MVA.

4. To assess the toxicity of immunization with 5T4-MVA.

5. To assess the level of 5T4-specific antibody response to immunization with 5T4-MVA.

6. To investigate in a preliminary manner the association of 5T4-MVA immune response with progression-free survival at 3 and 12 months.

7. To determine the incidence of 5T4 expression in tumor samples from patients enrolled in the trial and investigate the association of tumor 5T4 expression and OS and PFS.

8. To investigate the association of the tumor infiltrating lymphocyte and CD1a+ dendritic cell density and the development of 5T4-specific T cell immunity.

Patient Population

Our targeted population for this study will be Stage IIIB, Stage IIIC, and Stage IV breast cancer patients who have received standard therapy and are now in a state of minimal residual disease or NED. Despite the heterogeneity in this population of advanced stage patients, both of these groups have demonstrated similar PFS and are at high risk of relapse. The current published literature reports similar PFS in this patient population with the median PFS reported as 18 - 22 months for both of these groups. Similarly, results from a recent SWOG neoadjuvant clinical trial (**S9625**) showed a significant difference in PFS of patients with inflammatory breast cancer (Stage IIIB) versus those patients with locally advanced disease (Stage IIIA). The median PFS of the Stage IIIB group was 18 months which is similar to that of Stage IV patients.

Study Design

The primary objective of this study will be to determine the feasibility of conducting a live viral vaccine trial in the Stage IIIB, IIIC, IV NED breast cancer population in the cooperative group setting. Primarily, feasibility will be assessed both by accrual rate and by the percentage of patients successfully receiving a full vaccination.

One hundred-twenty eligible patients will be accrued. Full accrual is expected within 2 years to this limited institution study. If accrual is less than 30 patients by the end of the first year, or less than 90 patients by the end of the second year, the study will be closed and accrual will be considered insufficient to warrant a Phase III study within the Southwest Oncology Group.

A complete vaccination will be defined as receiving all 3 of the primary vaccine series injections and at least 1 of the booster vaccine injections. The study will be considered feasible if 85% of the eligible patients registered receive a full vaccination, and would not be considered feasible if only 75% or less receive a full vaccination. If 98 or more patients are observed receiving a full vaccination, this will be considered evidence that the study is feasible with respect to delivery of a full vaccination of 5T4-MVA. This design has a power of 87% and a significance level of 5%.

Dose and Schedule

Vaccine Dose and Treatment Schedule: Primary Vaccine Series

AGENT	DOSE	ROUTE	RE-RX INTERVAL	NOTES
5T4-MVA	1 x 10^9 $TCID_{50}$/mL	intramuscular	monthly x 3 months (Month 1, 2, 3)	*Injections will be given to the same general area each month.

Vaccine Dose and Treatment Schedule: Booster Vaccine Series

AGENT	DOSE	ROUTE	RE-RX INTERVAL	NOTES
5T4-MVA.	1 x 10^9 $TCID_{50}$/mL	intramuscular	every 3 months post initial series x 3 (months 6, 9, 12)	*Injections will be given to the same general area each month.

* Vaccinations will be administered intramuscularly into the deltoid muscle of the upper arm. If a subject has undergone axillary node dissection the vaccine will be administered to the contralateral side. If the subject has undergone bilateral axillary node dissections, the vaccine will be administered on the lateral thigh or buttock.

Endpoints

There is limited published data on the duration of PFS in this patient population and it will be important to characterize this in the current trial before embarking on larger randomized clinical trials. With 120 patients, the probability of 18-month progression-free survival can be estimated to within ± .09 (95% confidence interval). In addition, for estimating the progression-free survival rate at any selected time points, say 1 or 2 years, the width of the 95% confidence interval will be at most ± .09. This would ensure an estimate with adequate precision for comparison with the best available published data when the study is completed in approximately 2-3 years, and for planning the appropriate next investigational step.

Safety will be monitored by physical examination, laboratory evaluations, and assessment of adverse events. Patients will be monitored for progression-free survival and overall survival.

Product

TroVax® is derived from a replication incompetent vaccinia virus called modified vaccinia Ankara MVA that was developed as a safe vaccine for smallpox.

Mechanism of Action: Expression vector to deliver a human gene encoding the 5T4 oncofoetal antigen. The poxvirus vaccines work by entering human cells, expressing genes that are processed via the antigen presentation system and then killing the cell to release the cocktail of expressed proteins (cytolysis). In the case of MVA only the initial cells that take up the vector are killed, the cytolytic effect does not spread because the vector cannot replicate. The damage to the cells is essential to generating a strong immune response and is thought to be the reason for the potency of this class of vectors.

TroVax® was safe and well tolerated at all doses and no serious adverse events were reported as being related to the vaccine. Minor adverse events, which were reported as attributed to TroVax, were irritation at the injection site in six patients, hot sweats in two patients and loss of appetite in one patient. All resolved quickly.