

### **A.3.4 Non-Technical Abstract**

A Phase I Vaccine Safety and Chemotherapy Dose-Finding Trial of an Allogeneic GM-CSF-secreting Breast Cancer Vaccine Given in a Specifically Timed Sequence with Immunomodulatory Doses of Cyclophosphamide and Doxorubicin

Breast cancer ranks second among cancer deaths in women (American Cancer Society, 2005). In the year 2005, the American Cancer Society has estimated that 212,240 new invasive cases of breast cancer will be diagnosed, and predicts 40,410 deaths will result from breast cancer. While 80% of patients present with locoregional disease involving the breast and/or axillary lymph nodes, about half develop disseminated disease and ultimately die from it. Stage IV breast cancer is typically managed with hormonal agents or conventional cytotoxic drugs. Tumors quickly become resistant to these treatments, however, underscoring the need for novel therapeutic strategies that can be integrated with existing therapeutic modalities in an additive or synergistic fashion. Immunotherapy is a particularly attractive strategy for overcoming drug resistance. Immunotherapy is a type of treatment for cancer based on the idea that the immune system can be activated to destroy cancer cells that might be resistant to hormonal therapy and chemotherapy. A vaccine is a kind of immunotherapy that delivers an antigen (something that activates the immune system) so that the immune system recognizes cells with that antigen as foreign and destroys any cells that display that antigen.

The allogeneic breast tumor cell vaccine consists of two types of breast tumor cells developed from the tumor cells of patients with breast cancer. The human granulocyte-macrophage colony-stimulating factor (GM-CSF) gene was used to genetically modify the breast tumor cells to secrete GM-CSF. GM-CSF is a substance made by the body that helps the immune system recognize a tumor and destroy it. The vaccine cells were irradiated to prevent them from growing or dividing. The cells themselves are not radioactive. The cells are stored frozen until the day of vaccination. The total number of cells in each vaccination will be 500,000,000, divided into twelve injections given in the thighs and arms. The choice of twelve injections for each vaccination is based on the volume of the vaccination and a finding that the body has a better chance to respond to the vaccine if it is injected into a number of different areas.

We propose to test the safety and bioactivity of an allogeneic GM-CSF-secreting breast cancer vaccine when given in a specifically timed sequence with Cyclophosphamide (CY) and Doxorubicin (DOX), two drugs commonly used to treat breast cancer. In this study the CY and DOX are used at lower doses than usual to help the vaccine to activate the patient's immune system. The doses and scheduling of CY and DOX used are based on testing the drugs with a GM-CSF-secreting vaccine in mice that get breast cancer, and are the ones that enabled the vaccine to induce the most potent anti-tumor immunity. The dose of vaccine cells is based on the safety of the same dose of a similar GM-CSF-secreting vaccine for pancreatic cancer. Patients will receive a fixed dose of the allogeneic breast tumor vaccine consisting of two irradiated allogeneic breast cancer cell lines transfected with the GM-CSF gene in a specifically timed sequence with a range of low doses of CY and DOX. Patients will receive CY intravenously on Day -1, vaccination on Day 0, and DOX intravenously on Day +7.

Patients will receive three monthly vaccination cycles, with a fourth and final (boost) vaccination cycle three months from the third cycle.

Blood samples to measure GM-CSF levels will be taken on the day of vaccination and then every day for 4 days. Blood samples to evaluate the safety of the vaccinations will be taken once a week for one month following each vaccination. Blood samples may be taken near the patient's home and sent to Johns Hopkins for testing. During studies of similar vaccines in renal cell cancer, prostate cancer, pancreatic cancer, and non-small cell lung cancer, local symptoms of swelling and redness developed at the vaccine site between 2 and 7 days after vaccination. In this study, if the patient's vaccination site shows swelling over 1 cm in diameter, a skin biopsy will be taken. The skin biopsy will be evaluated to determine to what types of cells are important to the immune response. Based on our previous preclinical and clinical data, the biopsy will be taken on day 3, and possibly on day 7, after vaccination. Other tests and evaluations include history and physical examination, vital signs, CT of the chest, abdomen, and pelvis, nuclear medicine bone scan, pre-vaccination biopsy, blood for immune monitoring, and a skin test for delayed-type hypersensitivity (DTH) that is like a PPD test and involves injecting pieces of a protein antigen (HER-2/neu) that is delivered by the breast cancer vaccine. The purpose of the DTH test is to evaluate whether the patient has developed a systemic immune response to the breast cancer vaccine.

To date, 15 of a planned 30 patients have been vaccinated; the first 6 patients received vaccine alone, and the remaining 9 patients have received vaccine in sequence with Cyclophosphamide (CY) and Doxorubicin (DOX). We have already completed all vaccinations on the first 11 patients vaccinated on study, 7 of whom received all 4 vaccinations and 5 remain disease-free. Four patients showed disease progression while on study and therefore did not receive all vaccinations. One of these patients died of metastatic breast cancer 10 months after receiving her last vaccination. Her death was unrelated to the vaccine. Four patients remain on study. There have been no serious adverse events related to the vaccine. The study is still open to accrual with the goal of accruing 30 research subjects.