

Non-Scientific Abstract:

Cancer is a leading cause of death in the Western World. Current cancer therapy includes surgery, chemotherapy, and radiation therapy (RT). These treatments, either alone or in combination, provide high degrees of local control in early stage disease but often fail in eradicating bulky tumors. This ultimately leads to spread of the disease. The addition of gene transfer to these currently available treatments provides the potential to improve control of these tumors and possibly lead to longer survival.

Pancreatic cancer is one of the most lethal tumor types in the Western World. About 29,000 people are newly diagnosed with pancreatic cancer in the United States. The long-term survival from this disease remains poor and typically less than 3% of patients remain alive 5 years after the initial presentation. Curative surgical resection is most often not possible because of the aggressiveness of this tumor and the propensity to spread to other areas. Combination therapy of radiation and chemotherapy is an established strategy for treatment of patients with inoperable cancer of the pancreas. These strategies improve local control and survival, but the majority of the patients will develop local recurrence and/or distant spread of disease and die. There has been great interest in new combination treatment strategies that improve local control, or reduce the spread of disease. The rationale for the proposed study is that the combination of radiation therapy, Fluorouracil (5-FU) and intratumoral injection of TNFerade may improve local control, reduce recurrences and improve quality of life and survival in patients with this disease.

The study will consist of two parts. The first part is called the dose-escalation phase. Dose escalation means that increasing amounts of the drug will be given to different groups of patients to determine the maximum dose of study medication that can be given. During this part of the study, up to 15 patients will participate. Once this part of the study is completed, the second part of the study is designed to compare the combination of TNFerade™ with 5-FU and radiation therapy, to 5-FU and radiation therapy alone. 5-FU and radiation therapy are considered standard therapy for this type of cancer. In this part approximately 120 patients will participate.

TNFerade™ biologic will be administered by injection directly into the tumor using either endoscopic ultrasound- guided fine needle injection from a tube in the stomach or CT-guided injection through the skin. The selection of delivery method for an individual clinic will be made according to that site's preference. Up to three dose levels will be explored in the dose escalation phase. TNFerade™ will be injected during five weekly injection sessions, followed by radiation therapy. 5-FU will be administered by continuous intravenous infusion, five days a week, starting on the first day of radiation therapy.

The objective of this study is to assess the safety and potential activity of TNFerade™ in combination with 5-FU and radiation therapy for first-line treatment of inoperable locally advanced pancreatic cancer. For the safety measurements, various laboratory tests will be employed to monitor the study subjects. In addition, the subjects will be followed to see

if there are adverse effects of the treatment. To see if the treatment is working, the tumors will be measured to look for differences in tumor shrinkage and survival between the different groups in the second part of the study. Subjects will also be followed to evaluate other clinical benefit related responses (weight loss, performance status, pain, pain medication consumption).