

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.

Esophageal cancer, in particular, is highly lethal. The 5-year survival of all patient ranges from 2 to 10%. There are two standards of care for these patients, surgery alone or chemotherapy and radiation (chemoradiation) given at the same time. At time of presentation, surgery is appropriate for about half of the patients who have localized disease, while the rest are not appropriate surgical candidates due to complications of their cancer. However, the five-year survival rate is low following surgery, therefore, there has been a high interest in adding preoperative treatments prior to surgery.

In this protocol, we will combine TNFerade™, an adenoviral gene transfer vector that expresses TNF- α , an anti-cancer protein, with preoperative chemoradiation. TNFerade™ contains genetic elements that are controlled by radiation so that the expression of the TNF- α anti-cancer protein is produced at the site of the cancer but not so much gets into the body as to cause toxic side effects.

The population for this study will be newly diagnosed adult subjects with locally advanced esophageal cancer (stage II and III) limited to the esophagus and regional lymph nodes who have not received prior treatment and are considered surgical candidates. Patients with metastatic disease or patients with confirmed invasion of the bronchial tree or aorta at time of screening are not eligible.

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 18 patients will participate. Once this part of the study is completed, the second part of the study is designed to look for the absence of tumor tissue in the material removed after the surgery in 53 patients using the dose determined in the first part of the study. If more than half of the patients have no tumor tissue left, it will be concluded that TNFerade™ is active against cancer in patients with this disease. Note that the study will be stopped if in the first 26 of these patients fewer than 7 show an absence of tumor tissue following surgery, as it will be concluded that it is not likely that the goal of more than half of 53 patients being free of tumor tissue will be reached.

The procedure for this study will be that patients undergo treatment consisting of chemoradiation [external radiation therapy (RT), fluorouracil (5-FU) and cisplatinol], combined with intratumoral injection of TNFerade™ biologic via endoscopic guided injection for several weeks before surgery. Up to 5 weekly TNFerade injections will be

administered as tolerated. TNFerade™ will be initiated on the same day that chemoradiation is started. Patients will undergo total removal of the area affected by the tumor (esophagogastrectomy) at 4 to 10 weeks after completion of radiation. As described above, the primary goal of the study is to look for the absence of tumor tissue in the material removed during the surgery. In addition, other study objectives include assessments of how long these patients survive, how long until their tumor reappears in addition to the overall safety and side effects of the treatment.