

1. Scientific ABSTRACT

Pancreatic cancer is the fourth leading cause of cancer death in the United States and has one of the worst prognoses of any malignancy. In 2004, it is estimated that 31,860 new cases will be diagnosed and 31,270 deaths will occur from pancreatic cancer. Almost every patient with pancreatic cancer will develop metastases and die. For all stages combined, the median survival is 9-12 months and overall five-year survival rate is 3%. Currently, surgery is the only potentially curative intervention, but the majority of patients with pancreatic cancer, however, present with locally advanced (unresectable) or metastatic disease. Standard treatment for locally advanced, nonmetastatic, unresectable disease is fluorouracil (5-FU) and external beam irradiation. Despite treatment with chemoradiation in patients with locally advanced or microscopic residual disease, median survival is only about 10-11 months. More effective treatments (for both local tumor control and systemic disease) are clearly needed.

This trial seeks to determine whether the combination of 5-FU based chemoradiation therapy and a novel tumor vaccine (PANVACTM-VF) with recombinant GM-CSF would extend the overall survival rate and progression-free survival in patients with unresectable, locally advanced pancreatic cancer, as compared to what would be expected from standard 5-FU-based chemoradiation therapy alone. 5-FU is typically given as a continuous infusion 5-7 days a week for the duration of radiation therapy. Patients enrolled in the trial will receive PANVAC-V (recombinant vaccinia vaccine containing the genes encoding for CEA and MUC-1 along with the costimulatory molecules, LFA-3, CAM-1 and B7.1) with GM-CSF. PANVAC-V and GM-CSF will be given subcutaneous each at the start of the study. Two weeks later, patients will start chemoradiation treatment and will receive the first of a series booster vaccination with PANVAC-F (recombinant fowlpox vaccine containing the same genes as PANVAC-V) and GM-CSF. Booster vaccinations and low-dose GM-CSF injections will be given every 2 weeks during the chemoradiation treatment. After completion of chemoradiation, patients will continue on-trial and receive two week cycles of capecitabine (Xeloda) every three weeks (2 weeks on, one week off) starting after 3-6 weeks of completion of 5-FU-radiation therapy. Capecitabine will be administered for 6 months (8 cycles). PANVAC-F booster vaccinations will be administered every three weeks coinciding with the first dose of capecitabine and will continue for 6 months.

The immunotherapeutic approach provided in this trial in conjunction with standard of care treatment for unresectable pancreatic cancer is based on the previous experience with these and related pox-vector-based vaccines in terms of limited toxicity and ability to induce immune responses to TAA in patients with advanced carcinomas. CEA and MUC-1 are overexpressed in virtually all adenocarcinomas of the pancreas and pox viral vectors, such as PANVAC-VF, have been shown to induce immune response to these tumor antigens. It has also been shown that radiation and 5-FU can both upregulate Fas on tumor cells and potentiate T-cell mediated killing of tumor. Furthermore, irradiated tumor cells upon dying may release a variety of tumor-related antigens that could amplify the tumor-specific immune response. Our preclinical studies have demonstrated that stimulation of dendritic cells (DC), following primary tumor irradiation, induced a strong tumor-specific immune response that eradicated distant metastases in murine models of lung adenocarcinoma and hepatoma and improved survival in these models. 5-FU does not inhibit cellular or humoral immune responses when given with a vaccine. Additionally, 5-FU induces the cell surface expression of CEA. Finally, the use of vaccine and radiation is safe in preclinical models and in patients in ongoing clinical trial. A phase I study using PANVAC-VF in combination with GM-CSF in patients with unresectable adenocarcinoma of the pancreas has shown the treatment regimen to be safe.