

Scientific Abstract

Objectives:

Primary:

1. To evaluate the safety of primary and boost vaccinations with lethally irradiated allogeneic pancreatic tumor cells transfected with the GM-CSF gene vaccine in the treatment of patients with surgically resected adenocarcinoma of the head, neck, or uncinata of the pancreas

Secondary:

1. To estimate the association of specific *in vivo* parameters of immune response including, but not limited to mesothelin, prostate stem cell antigen (PSCA), and mutated *k-ras*-specific T cell responses, with clinical responses in patients who are receiving semi-annual vaccine boosting with lethally irradiated allogeneic pancreatic tumor cells transfected with the GM-CSF gene.

2. To estimate the efficacy of vaccine boosts in the treatment of patients with adenocarcinoma of the pancreas in terms of overall and recurrence free survival.

3. To use the serum GM-CSF levels as a measure of longevity of an allogeneic vaccine following an semi-annual boosting with lethally irradiated allogeneic pancreatic tumor cells transfected with the GM-CSF gene.

4. To determine the psychosocial and symptom profiles of patients with pancreatic cancer treated with an irradiated allogeneic GM-CSF secreting vaccine, and to explore changes over time. The psychosocial profile will include information about, but is not limited to demographics, quality of life, hope, trust, social support, decision control and advanced directives. The symptom profile will include but is not limited to pain, anorexia, fatigue, and mood state.

Study population:

In order to be considered for this study, patients need to meet following major criteria for inclusion:

- History of surgically resected pathologic stage 1 (no direct tumor extension beyond pancreas and no regional lymph node metastases), 2 (direct extension of tumor beyond pancreas), and/or 3 (regional lymph node metastases) adenocarcinoma of the head, neck, tail, or uncinata of the pancreas.
- Have no radiographic evidence of pancreatic cancer disease recurrence.
- Have not received any anti-cancer therapy in the past 28 days.

Study Design:

Eligible subjects will receive by intradermal administration the pancreatic tumor vaccine consisting of two irradiated, allogeneic pancreatic tumor cell lines transfected with the granulocyte macrophage-colony stimulating factor (GM-CSF) gene.. There will be two cohorts of research participants: those who have previously received the pancreatic cancer vaccine (up to

17) and those who are vaccine naïve (30-40). For those patients who have received the vaccine, the boosts will be offered as a continuation of care. For those patients who are vaccine naïve, the feasibility of investigating the use of vaccine priming and boosting to prolong disease free status will be tested. Up to 100 patients may be consented to obtain the targeted accrual goal.

For research participants who have previously received the pancreatic cancer vaccine, the first vaccine boost will be given at least six months after the anniversary date of their last vaccination (+/- 30 days). Since the last vaccination date from the parent vaccine study for some subjects has occurred more than one year ago, they may establish a new semi-annual dates for vaccine boosting. One of the semi-annual vaccine boost dates will be the same as their annual long term-follow-up visit date..

For research participants who are vaccine naïve, their first vaccine will be given at least 28 days after their last anti-cancer therapy. The vaccine naïve research participant will receive priming vaccinations once every month for a total of three vaccines, and then will receive the vaccine boosting on a semi-annual basis.

The vaccine will be administered once every six months (+/- 30 days) after the previous vaccine until the subject no longer meets the eligibility criteria, no longer wishes to participate in the study, or the vaccine supply is exhausted. In the event that the eligibility criteria are not met, the subject may be re-evaluated if the Principal Investigator anticipates that the research participant may meet the eligibility criteria later. If eligibility is later established, a new anniversary date for vaccine boosting and long-term follow-up will also be set as the date of the most recent vaccination.

The psychosocial and symptom responses will be measured through:

EORTC QLQ-C30

City of Hope Quality of Life, Cancer patient/survivor version, QOL-CA

Herth Hope Index

Symptom Distress Scale

Trust Scale

Pancreatic Cancer Survivor Survey

Study Drug:

The vaccine consists of equal numbers (2.5×10^8 each) of Panc 6.03 and Panc 10.05 cells combined into a single vaccination. The final vaccine population secretes 100 ng/ 10^6 cells/ 24 hours of bio-active GM-CSF. Vaccine cells from each pancreas tumor cell line frozen at 1.25×10^8 cells/vial (2 vials per cell line) in an injectable formulation of Pentaspan (10% Pentastarch in 0.9% sodium chloride with 2% human serum albumin and 5% DMSO) will be thawed on the day of vaccination, irradiated with 150 Gy and taken up into syringes. Each vaccination will consist of six total intradermal injections, two each in the right and left thighs, and two in the non-dominant arm. In the event that the specified limb is contraindicated, the dominant arm may be used. The vaccine consists of equal numbers (2.5×10^8 each) of Panc 6.03 and Panc 10.05 cells. The combined 5×10^8 cells of Panc 6.03 and Panc 10.05 cells will be divided evenly amongst 6 syringes for intradermal injection.

Eligibility Criteria

Eligibility to receive a vaccination must be determined with the first vaccination (section 3.2.2. and 3.2.3) and then again with each semi-annual boost vaccination (section 3.2.4 and 3.2.5.) by the Principal Investigator or his designee prior to the administration of the research product. There will be no re-evaluation of eligibility for the second and third priming vaccines for the vaccine naïve cohort.

If the eligibility criteria for vaccination are not met the research participant may be re-evaluated if the Principal Investigator anticipates that the research participant may later meet the eligibility criteria. There is no time limit. If vaccination eligibility is later established, new semi-annual dates for vaccine boosting and long term follow-up will be re-set as the date of the most recent vaccination.

Inclusion Criteria for the First Vaccination:

Research participants must meet the following criteria.

1. Have a history of surgically resected pathologic stage 1 (no direct tumor extension beyond pancreas and no regional lymph node metastases), 2 (direct extension of tumor beyond pancreas), and/or 3 (regional lymph node metastases) adenocarcinoma of the head, neck, tail, or uncinata of the pancreas.
2. Received the last lethally irradiated GM-CSF transfected allogeneic pancreatic cell lines Panc 10.05 and Panc 6.03 as a participant in either one of the Hopkins IRB protocols: application number 96-01-25-01 entitled “A Phase I Clinical Trial of Lethally Irradiated Allogeneic Pancreatic Tumor Cells Transfected with the GM-CSF Gene for the Treatment of Adenocarcinoma of the Pancreas”, SKCCC J9617, or application number 00-01-13-02, entitled “A Safety and Efficacy Trial of Lethally Irradiated Allogeneic Pancreatic Tumor Cells Transfected with the GM-CSF Gene in Combination with Adjuvant Chemoradiotherapy for the Treatment of Adenocarcinoma of the Pancreas”, SKCCC J9988, at least 6 months ago;

OR

Completed adjuvant chemoradiation therapy at least 28 days prior.

3. Received the last anti-cancer therapy at least 28 days ago.
4. Provide informed consent.
5. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
6. Have adequate hematologic function (Hemoglobin \geq 9 gm/dl, ANC \geq 1500 #/cu mm, platelets \geq 100,000 K/cu mm)
7. Have adequate renal function (Serum creatinine \leq 2 mg/dL).

8. Have adequate hepatic function (Bilirubin \leq 2.0 mg/dL, unless known Gilbert's Syndrome; AST, ALT and amylase \leq 2x upper limit of normal: Alk Phos \leq 5x upper limit of normal.)

9. Agree to use adequate birth control, if of childbearing potential.

Exclusion Criteria for First Vaccination:

Research participants with any of the following will be excluded from study entry:

1. Radiographical evidence of pancreatic cancer disease recurrence.
2. Documented history of autoimmune diseases including systemic lupus erythematosus, sarcoidosis, rheumatoid arthritis, glomerulonephritis, or vasculitis.
3. Uncontrolled medical problems.
4. Systemic steroid therapy within 28 days before vaccine administration.
5. Anticipated need for systemic steroid therapy within 28 days after vaccine administration.
6. Evidence of active infections.
7. Pregnant.

Inclusion Criteria for Boost Vaccination:

Research participants must meet the following criteria.

1. Received the last lethally irradiated GM-CSF transfected allogeneic pancreatic cell lines Panc 10.05 and Panc 6.03 at least six months prior (+/- 30 days).
2. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
3. Have adequate hematologic function (Hemoglobin \geq 9 gm/dl, ANC \geq 1500/cu mm, platelets \geq 100,000/cu mm)
4. Have adequate renal function (Serum creatinine \leq 2 mg/dl).
5. Have adequate hepatic function (Bilirubin \leq 2.0 mg/dl, unless known Gilbert's Syndrome; AST, ALT and amylase \leq 2x upper limit of normal: Alk Phos \leq 5x upper limit of normal.)
6. Agree to use adequate birth control, if of childbearing potential.

Exclusion Criteria for Boost Vaccination:

Patients with any of the following will be excluded from study entry or will not be able to continue:

1. Radiographical evidence of pancreatic cancer disease recurrence.
2. Documented history of autoimmune diseases including systemic lupus erythematosus, sarcoidosis, rheumatoid arthritis, glomerulonephritis, or vasculitis.
3. Uncontrolled medical problems.
4. Systemic steroid therapy within 28 days before vaccine administration.
5. Anticipated need for systemic steroid therapy within 28 days after vaccine administration.
6. Evidence of active infections.
7. Pregnant.

Study schema including toxicity assessments and immune monitoring.

Assessment	Day 0	Day 1	Day 2	Day 3	Day 4				Day 28
Clinical evaluation ²	X								
CT abd/chest/pelvis ²	X								
Vital signs ³	X	X		X					
Toxicity assessment/evaluation ⁴	X	X		X ⁴					X ⁴
Vax site assessment ⁴		X		X ⁴					X ⁴
Heme/ diff/abs.eos ²	X	X							
Chemistries ⁶	X								
CA 19-9 ²	X								
Amylase ²	X								
GM-CSF level	X	X	X	X	X				
Leukapheresis or PBL <i>in vitro</i> studies ^{2, 10}	X								
Research blood: HLA typing and EBV testing ⁷	X								
Research blood: Serum banking ⁸	X								
Vaccine site biopsy ⁸	X ⁹			X					
Photograph, if indicated ⁸	X	X		X					
Measurement tools/ Surveys ¹⁰	X								X

¹ Day 28 assessments will be done as the off-study visit, whenever possible. If the research participant goes off-study within 28 days of the last day 28 visit, the off-study visit will not be repeated.

- ² May be done up to two weeks prior to Day 0 and at day 28 of the first and semi-annual vaccinations. Additional leukapheresis may be performed for an interesting immunological response.
- ³ Vital signs include temperature, pulse rate, respiration rate, and blood pressure
- ⁴ Assess to resolution.
- ⁵ Information may be obtained by phone and/or through the evaluation by the local health care provider.
- ⁶ Chemistries include: electrolytes, BUN, creatinine, AST, ALT, total bilirubin, and alkaline phosphatase
- ⁷ Prior to first vaccination only, HLA typing and EBV testing will be obtained on vaccine naïve participants only..
- ⁸ At anytime during the study, additional leukapheresis or PBL *in vitro* studies may be obtained, skin biopsies and photographs may be taken of the vaccine sites and rashes, as clinical indicated as long as the research participant is in agreement.
- ⁹ Obtain baseline biopsy prior to the first vaccine only for the vaccine naïve cohort only.
- ¹⁰ Measurement tools/surveys include: EORTC QLQ-C30, City of Hope Quality of Life, Cancer patient/survivor version, QOL-CA, Herth Hope Index, Symptom Distress Scale, Trust Scale. Pancreatic Cancer Survivor Survey. Tools/surveys may be mailed to the research participant's home with a stamped return envelope.