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A Safety and Efficacy Trial of Vaccine Boosting with Lethally Irradiated Allogeneic Pancreatic Tumor Cells Transfected with the GM-CSF Gene for the Treatment of Pancreatic Adenocarcinoma

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1.0 Study Synopsis

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 uncinate 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 a 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 uncinate 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 (30-45). 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. As of Amendment #9, participants will be switched to annual vaccinations. One of the semi-annual or 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. As of Amendment #9, participants will be switched to annual vaccinations.

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. As of Amendment #9, participants will be switched to annual vaccinations (+/- 30 days). 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.

In the event that a research participant has evidence of persistent vaccine-related responses (including, but not limited to: vaccine site flares such as recurrent erythema, induration, and pruritus at previous vaccine administration sites; urticaria) occurring at the frequency of more than once in the previous three months, the research participant may choose to delay the semi-annual or annual boost vaccination for up to one year after the last vaccine-related response. The research participant may also choose to continue to receive the semi-annual or annual boost vaccinations per protocol with evidence of persistent vaccine-related responses. Research participants experiencing urticaria must wait at least one month since the last hive before receiving another vaccine.

Study Drug:

[redacted] 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 x

10^8 cells of Panc 6.03 and Panc 10.05 cells will be divided evenly amongst 6 syringes for intradermal injection.

2.0 Background and Rationale

2.1 Introduction

Pancreatic cancer is the fourth leading cause of all cancer deaths. Although only 33,730 Americans are expected be diagnosed with pancreatic cancer, 32,300 will die from pancreatic cancer in 2006 (American Cancer Society, 2006). Only about 20% of patients diagnosed with pancreatic cancer will be eligible for surgical resection with a pancreaticodudectomy, the only potentially curative treatment. However, even among those patients who undergo surgery and adjuvant therapy 79% will eventually die of recurrent disease (Ahlgren, 1996). Pancreatic cancer has the most dismal prognosis among 18 cancer diagnoses. The statistics for 1995-2000 for the five- year relative survival rates for pancreatic cancer by stage are: 4.4% for all stages, 15.2% for localized, 6.8% for regional, and 1.8% for distant (American Cancer Society, 2006). Despite significant efforts to develop new therapies, locally advanced unresectable disease has a median survival of 10-12 months and subjects with metastatic pancreatic adenocarcinoma have a median survival of 3-6 months. While surgical resection is the only curative option, the majority of subjects (80-85%) unfortunately present with advanced unresectable disease. These dismal survival rates support the development of novel approaches for the treatment of pancreatic cancer.

2.2 Rationale for Cell-Based Immunotherapy of Pancreatic Adenocarcinoma

Adjuvant chemoradiation with a 5-Fluorouracil (5-FU) containing chemotherapy regime has been the gold standard for patients undergoing complete pancreatic cancer resection. However, even the most recent studies have demonstrated only modest improvements in disease-free survival (Smeenk, Tran, Erdmann, van Eijck, & Jeekel, 2005). Immunotherapy is a potentially therapeutic approach to the treatment of pancreatic adenocarcinoma for several reasons. First, immunologic killing of tumor cells acts by a mechanism that is distinct from standard chemotherapy and radiation therapy, and thus may represent a non-cross resistant treatment modality. Second, the immune system is capable of recognizing a broad diversity of potential antigens while orchestrating selective and specific cytotoxic responses, two features that may be particularly important in killing a heterogeneous tumor population while avoiding normal tissue toxicity. Third, preclinical animal models using a vaccine approach for immunotherapy have been able to eliminate small burdens of established tumors, a situation that corresponds to the state of minimal residual disease commonly found after resection of human tumors (Burris, Moore, Cripps et al., 1997; Heineman, Quietzsch, Giesler et al., 2003). Fourth, a completed Phase I trial evaluating an allogeneic, irradiated, granulocyte-macrophage colony stimulating factor (GM-CSF) secreting tumor vaccine in patients with adenocarcinoma of the pancreas demonstrated both clinical and immunologic responses (Jaffee et al., 2001). This study, together with the increasing evidence that human tumor-specific antigens can be recognized by the immune system, strongly suggests that specific immune responses can be generated against pancreatic adenocarcinoma if the immune system is sufficiently primed.

An early analysis of a follow-up 60 patient study testing the safety and efficacy of the highest dose of vaccine tested in the above-mentioned phase I study, has shown an 88% one-year survival and a 78% two-year survival. A proportion of patients from both the phase I and the phase II studies remain disease-free. This current trial is designed to test the hypothesis that boosting with an allogeneic paracrine cytokine tumor vaccine induces immune responses that are associated with a continuous pancreatic cancer free survival.

2.3 Vaccine-Based Strategies Currently Undergoing Testing in Subjects with Pancreatic Adenocarcinoma

There are a number of vaccine approaches that have been tested or are undergoing testing in pancreatic cancer subjects. Most of these approaches target one candidate tumor antigen. Such targets include: MUC-1, CEA, and mutated k-ras. The approaches used have included immunization with HLA class I and class II peptides, immunization with the whole protein, or delivery by antibody, heat shock protein or dendritic cells (Apostolopos & McKenzie, 1994; Kabayashi, Terao, & Kawashima, 1992; Brossart, Heinrich, & Stuhler, 1999; Apostolopous, Karanikas, Haurum et al., 1997; Abrams, Hand, Tsang et al., 1996). To date, these studies have demonstrated the induction of T cell responses. Significant clinical responses have not yet been observed. This may be due to the lack of potency of these approaches, to the existence of host mechanisms of immune tolerance, or both. More recent pre-clinical studies suggest that combined vaccine approaches integrating vaccine with immunomodulatory agents are significantly more effective than vaccines alone in models of tumor tolerance.

2.4 Rationale for the use of a GM-CSF secreting whole cell vaccine approach

We have developed a cytokine secreting tumor vaccine approach that can cure mice of pre-existing tumors. This approach is based on the concept that certain cytokines are required at the site of the tumor to effectively prime cancer-specific immunity. In the only study to directly compare a large number of immune stimulating cytokines, GM-CSF stood out as the most potent cytokine capable of inducing systemic anti-tumor immunity when expressed by the tumor cells for the initial 24-72 hours of immune priming. GM-CSF is now recognized to be the critical growth and differentiation factor for dendritic cells, the most potent professional antigen presenting cell responsible for priming immune responses against infectious agents and tumor antigens. Both autologous and allogeneic GM-CSF secreting vaccines have been tested in phase I and II trials in subjects with melanoma, renal cell, prostate, lung, breast and pancreatic cancers. Most of these studies demonstrated evidence of immune activation associated with clinical responses in 10-40% of treated subjects.

While the use of autologous tumor cells may preserve unique antigens expressed by each subject's cancer, the development of an autologous vaccine requires that extensive processing, in vitro expansion, and regulatory testing be performed for each individual subject vaccine. These limitations preclude the use of autologous cellular vaccine for most cancers including pancreatic adenocarcinoma. A growing body of evidence supports the immunologic rationale for using allogeneic tumor cells rather than autologous cells as the source of antigen used for the vaccination. First, studies evaluating human melanoma antigens have demonstrated that most of the human tumor antigens identified are shared among at least 50% of known human melanoma tumor cell lines, regardless of whether or not they share the same human leukocyte antigen (HLA) type (Cox,

Skipper, Chen et al., 1994; Kawakami, Eliyahu, & Delago, 1994). In addition, there is now both pre-clinical and human data in pancreatic cancer subjects treated with a GM-CSF vaccine to support host derived professional antigen presenting cells (APCs) as the critical cells required to present immunogen to T cells in the context of MHC (Dranoff, Jaffee, Golumbek et al., 1993; Jaffee, Hruban, Biedrzycki et al, 2001; Thomas, Santarsiero, Lutz et al., 2004). Therefore, the vaccine cells do not need to be HLA compatible with the host's immune system as long as they can release cellular proteins (the tumor antigens) for uptake by professional APCs (macrophages and dendritic cells) that are attracted to the vaccine site by GM-CSF. Taken together, the data suggest that relevant tumor antigens can be delivered by an allogeneic tumor and still sufficiently mount an effective immune response.

Two allogeneic cell lines have been developed from neoplastic tissue harvested from the surgical specimens of subjects undergoing pancreaticoduodenectomy at The Johns Hopkins Hospital. These cell lines have been characterized as 100% epithelial by cytokeratin staining (Jaffee, Abrams, Cameron et al., 1998). In addition, these cell lines carry the same k-ras mutation as the original tumor specimen that supports the conclusion that these lines are derived from malignant pancreatic tumor cells. The cell lines Panc 10.05 and Panc 6.03 both contain the most common k-ras mutation at codon 12 found in greater than 90% of pancreatic cancer. These lines secrete GM-CSF at 80-90 ng/ 10^6 cells/ 24 hrs for up to 5 days in culture (Jaffee, Abrams, Cameron et al., 1998; Jaffee, Drandoff, Cohen et al., 1993). These lines have undergone extensive regulatory testing and have been shown to maintain GM-CSF secretion, MHC class I levels, cytokeratin positive staining and the original K-ras mutation (Jaffee, Abrams, Cameron et al., 1998). These lines also express 2 new immunogenic pancreatic tumor antigens, mesothelin and PSCA. These lines have already been demonstrated to be safe and feasible to produce and administer in a phase I and two phase II studies in both the adjuvant and metastatic setting. The clinical lots for this study will be produced in the Johns Hopkins GMP Cell and Gene Therapy facility.

2.5 Biologic endpoints including pancreas tumor antigens such as mesothelin may serve as *in vitro* predictors of clinical response

The major limitation to developing cancer vaccines has been the lack of identified pancreatic tumor antigens that are the known targets of the immune response. As such, current immune based approaches either target a small group of candidate antigens expressed by the tumor or rely on whole tumor cells as the immunogen. However, with the recent sequencing of the human genome and the development of rapid methods for identifying genes that are differentially expressed by tumor cells (Iacobuzio-Donahue, Maitra, Shen-Ong et al., 2002), potential candidate immune targets are being discovered that may serve as immunogens for treatment as well as prevention. Recently, mesothelin, a transmembrane glycoprotein member of the mesothelin/megakaryocyte potentiating factor (MPF) family was identified by differential gene expression to be over-expressed by most pancreatic adenocarcinomas (Argani, Iacobuzio-Donahue, Ryu et al., 2001). More recently, mesothelin has been shown to be recognized by vaccinated uncultured $CD8^+$ T cells isolated from the three subjects who are long-term survivors from the previously described phase I GM-CSF pancreatic cancer vaccine study but not in the other subjects who received the vaccine but subsequently relapsed (Thomas, Santarsiero, Lutz et al., 2004). These data suggest that mesothelin may serve as an *in vitro* marker of vaccine induced T cell responses.

2.6 Rationale for Including Quality of Life Measurements

The significance of cancer survivorship and quality of life (QoL) has recently come to the forefront with the Institute of Medicine's (IOM) report (2005a). The IOM indicates "Survival rates are increasing, but no one knows at what cost to the health and well-being of cancer survivors." (IOM, page 1, 2005b).

Of the 33,730 Americans who are diagnosed each year with pancreatic cancer (American Cancer Society, 2006), those who are eligible for surgery are the most fortunate. While surgical resection is the only curative option, the majority (80-85%) have advanced unresectable disease at the time of diagnosis. Those patients who are eligible for surgical resection have a median survival of 18 months for pancreatic adenocarcinoma (Yeo et al., 1997) to 24 months for all malignant pancreas tumors (Billings et al., 2005). The threat of recurrence is real with many people having disease recurrence one year after surgery. The American Cancer Society's surveillance research indicates that the five-year survival for local pancreatic cancer is only 16%, and for all stages combined 5% (ACS, 2006). Overall, pancreatic cancer is one of, if not the most, feared cancers due to its dismal prognosis.

The impact of this ever-present threat of recurrence and uncertainty on health and QoL is under-researched. Recent studies have explored the long-term health consequences of some cancers, including head and neck (Mehanna & Morton, 2006), cervical (Wenzel et al., 2005), and breast cancer (Schou, Ekeberg, Sandvik, Hjermstad, & Ruland, 2005). However, the QoL and the health consequences of living with a cancer that is usually rapidly fatal are relatively unknown.

While cancer is the most ominous threat, other chronic conditions, such as diabetes that is surgically induced with a total pancreatectomy, may also impact the patient with pancreatic cancer. Billings (2005) surveyed a sample of 27 patients who had undergone a total pancreatectomy for either a benign and malignant pathology, and reported that their QoL was decreased compared to age and gender specific samples, but was similar to other people with diabetes.

This study will include past participants of the phase I and II pancreatic cancer vaccine research studies, as well as pancreatic cancer survivors who are pancreatic cancer vaccine naïve. There are three participants from the phase I study who remain pancreatic cancer free for more than eight years after diagnosis, including a working senior 72 years of age. While we believe that the pancreatic cancer survivors have good QoL we have yet to evaluate this with scientific rigor. Through qualitative research, Dr. D. Fitzsimmons found general consistencies between the perceptions of health care professionals and patients on QoL, but also noted differences (1999). Health care professionals think about QoL from a mechanistic view, focusing on the symptom impact, while patients incorporate coping as an essential component of their QoL (Fitzsimmons, George, Payne, & Johnson, 1999).

2.7 Phase I Study of Lethally Irradiated Allogeneic Pancreatic Tumor Cells Transfected with the GM-CSF Gene. Phase I Study at Johns Hopkins

2.7.1 Summary of Results

This study was the first clinical trial to test the hypothesis that allogeneic GM-CSF secreting pancreatic tumor cell lines can prime a systemic immune response in subjects with resected pancreatic adenocarcinoma. Fourteen subjects with stage 2 or 3 disease received an initial vaccination 8 weeks following resection. This was a dose escalation study in which 3 subjects each received 1 X 10^7, 5 X 10^7, and 1 X 10^8 vaccine cells. An additional 5 subjects received 5 X 10^8 vaccine cells. Study subjects were jointly enrolled in an adjuvant chemoradiation protocol for 6 months. Following the completion of adjuvant chemoradiation, subjects were re-assessed and those who were still in remission were treated with 3 additional vaccinations given one month apart at the same original dose that they received for the first vaccination. Toxicities were limited to grade I/II local reactions at the vaccine site, and self-limited systemic rashes, including one documented case of Grover's syndrome (Davis, Dineen, Landa et al., 1999). Systemic GM-CSF levels were evaluated as an indirect measure of the longevity of vaccine cells at the immunizing site. As was observed in pre-clinical studies, GM-CSF levels peaked at 48 hours following vaccination. In addition, serum GM- CSF levels could be detected for up to 96 hours following vaccination. These data, together with data from pre-clinical models, would suggest that detectable serum GM-CSF levels may serve as a bio-marker of immune response. The vaccine sites were also evaluated as a measure of the local immune reaction to the vaccine. Eleven of 14 subjects demonstrated a similar local inflammatory response to what has been observed in pre-clinical models and autologous GM-CSF vaccine clinical trials. Post-vaccination DTH responses to autologous tumor cells have been used in previously reported vaccine studies as a surrogate to identify and characterize specific immune responses that are associated with vaccination. In the pancreatic cancer vaccine trial, post-vaccination DTH responses to autologous tumor cells were observed in 1 of 3 subjects receiving 1 X 10^8 and in 2 of 5 subjects receiving 5 X 10^8 vaccine cells. Three long-term survivors of the initial phase I study are currently participants in the long-term follow-up study (IRB application number NA_00036444, J0248), remain disease-free and have expressed an interest in receiving additional vaccinations. No additional long-term toxicities have been uncovered in this cohort.

An ongoing Phase II clinical trial of the pancreatic cancer vaccine in subjects with operable pancreatic cancer who receive the vaccine after surgical resection of tumor and adjuvant radiation chemotherapy is currently being conducted at Johns Hopkins. The study recently completed enrollment of the 60 planned subjects. The toxicities associated with the vaccine in this study include: local vaccine site skin reactions and systemic rashes similar in severity (grade 1-2) to what was observed in the phase I trial.

2.7.2 Serum GM-CSF Levels

Serum GM-CSF levels were measured in the patients participating in the first pancreatic tumor vaccine study at time 0, 24, 48, 72, 96 and 120 hours following the first vaccine. The peak concentration of serum GM-CSF levels was seen at 48 hours in 83% (5/6) of the patients who achieved a measurable serum GM-CSF level. Only one patient who received dose level one had a measurable serum GM-CSF level at a minimum level of 1.0 pg/ml at 48 hours. There was no measurable serum GM-CSF level in any of the six patients who received dose levels two and three at any time point. All five patients who received dose level four had measurable serum GM-CSF

levels with the range of 1.2 to 14.0 pg/ml. GM-CSF levels became undetectable by 120 hours in all patients on study. No side effects other than asymptomatic eosinophilia were associated with these low but detectable serum GM-CSF levels.

2.7.3 Disease Free Survival

There are three patients who participated in the original study who remain pancreatic cancer disease free. The pancreatic cancer disease free survival of patients is defined as the time interval from date of diagnosis with adenocarcinoma of the pancreas to the date of radiographic evidence of disease recurrence. Only 14 of the 15 patients who participated in this trial were considered for the disease-free analysis, as one patient had stage 4 disease with liver metastasis prior to entering the study. An increase in the disease-free survival was associated with increasing total vaccine dose, which is equal to the dose level of cells multiplied by the number of doses, received. Using the nonparametric correlation of Spearman's rho the association of total pancreatic tumor vaccine dose and disease free survival is statistically significant (p=0.028).

Study participants had a 43% (6/14) one year disease free survival and 86% (12/14) one year overall survival. [redacted]

2.7.4 Toxicity Events

The most frequently occurring toxicities of the vaccine were injection site reactions. See Table 1 for a summary of the toxicities. All were grade 1 or 2 by the National Cancer Institute (NCI) Common Toxicity Criteria. The total number of injection site reactions in the phase I allogeneic pancreatic tumor vaccine study was 28 out of 30 (93%) vaccine treatments. Patients who received the second, third, and fourth dose levels of the allogeneic pancreatic tumor vaccine all had grade 2 injection site reactions. Of these grade 2 injection site reactions all had erythema and induration, with 69% (18/26) of the injection site reactions also having local pruritus at the vaccine sites. One patient experienced tenderness at the vaccine sites lasting up to three days after the first and third vaccine at dose level four. The patient required no analgesics. All injection site reactions were self-limiting and no one had any limitations on their activities of daily living related to these local signs and symptoms. Sixty-four percent (18/28) of the injection site reactions completely resolved within a week. Sixty-nine percent (9/13) of the patients who experienced injection site reactions were free of all local toxicities within a week. Thirty-one percent (4/13) of the patients experienced injection site reactions lasting more than a week with pruritus at the injection sites being the symptom of longest duration, lasting up to 41 days. Two of the four patients with the lengthy local toxicities also experienced systemic pruritus and rash. One of which was confirmed by biopsy to be Grover's Syndrome. The other person with the systemic rash and pruritus did not have a skin biopsy at that time. The same patient who experienced the Grover's Syndrome also developed recurrent swelling at the vaccine sites at that time which was seven to ten days after the second vaccine at level 4. After the third vaccine, this patient also had grade 1 lymphedema with erythema and swelling in the lymph drainage areas, particularly in the upper right extremity where two or the six vaccines were administered.

Systemic toxicities included: Grade 1 musculoskeletal stiffness and generalized pruritus lasting two hours. One patient on dose level 3 experienced acute anemia (hemoglobin dropped to 6.3 gm/dl), thrombocytopenia (platelets dropped to 5,800/mm^3), asymptomatic jaundice (total bilirubin increased to 9.8 mg/dl, direct bilirubin to 7.8 gm/dl). This occurred approximately six weeks after completing Mitomycin-C containing chemotherapy. There was also asymptomatic anemia with hematocrit nadir of 19.8 %, hemoglobin nadir 6.6 g/dl and asymptomatic thrombocytopenia with platelet nadir of 77,000 / mm^3 during the chemotherapy course which included Fluorouracil (5-FU), Leucovorin, Mitomycin-C, and Dipyridamole (Persantine) prior to this event. Therefore, these adverse events were consistent with Mitomycin-C associated thrombocytopenic purpura (TTP). Twenty-four days after second vaccine at dose level three, and seven days after the blood transfusions, the same person experienced a grand mal seizure. It is unlikely that this adverse event is related to the vaccine. After receiving the vaccine this patient developed symptoms that have since been attributed to thrombotic thrombocytopenic purpura (TTP). Although we believe this condition was due to the Mitomycin-C treatment completed one month previously, this was reported to the IRB as a possible adverse event due to the temporal proximity to immunization with the vaccine. The patient was taken off study. The patient's condition improved, the symptoms of TTP resolved, and the patient remains in complete remission at this time. This adverse event has not recurred on the 60 patient follow-up vaccine study.

With dose level four, 50% (3/6) patients experienced a systemic reaction. One patient experienced grade 1 constitutional symptom of fatigue and grade 1 musculoskeletal, and achy joints.
Another patient on vaccine dose level 4 experienced multiple vaccine related symptomatic toxicities, including: a grade 2 rash, systemic pruritus, and Grover's Syndrome, a grade 1 urticaria, and a grade 1 recall induration at the vaccine sites.

Table 1. Toxicity Events Associated with Phase I Allogeneic Pancreatic Tumor Vaccine

Total of thirty evaluated vaccine treatments. (Number of patients experiencing the toxicity)

Local Toxicities	Grade 1	Grade 2	Grade 3	Grade 4
Erythema at vaccine sites	1[a] (1)	26[a,b,c,d] (12)		
Induration at vaccine site		26[a,b,c,d] (12)		
Pruritus at vaccine sites	1[b] (1)	18[a,b,c,d] (11)		
Tenderness at vaccine sites		2[d] (1)		
Recall induration at vaccine sites	1[d] (1)			
Lymphedema of one extremity	1[d] (1)			

Systemic Toxicities	Grade 1	Grade 2	Grade 3	Grade 4
Pruritus (not vaccine sites)		3[b,d] (3)		
Urticaria		1[d] (1)		
Skin rash		2[d,e] (2)		
Joint stiffness/achy	2[b,d] (2)			
Fatigue	1[d] (1)			
Other[f]			1[c,f] (1)	1[c,f] (1)

N=15 patients

[a] Occurred after dose level one of 1×10^7 cells.
[b] Occurred after dose level two of 5.10×10^7 cells.
[c] Occurred after dose level three of 1.08×10^8 cells.
[d] Occurred after dose level four of 5.04×10^8 cells.
[e] One rash was biopsied to reveal Grover's syndrome.
[f] After receiving dose level three of 1.08×10^8 cells, one patient experienced Grade 2 thrombocytopenia, Grade 2 elevated SGOT (AST), Grade 3 seizure, Grade 3 anemia, Grade 3 elevated SGPT (ALT), Grade 3 elevated bilirubin. The symptoms have been attributed to thrombotic thrombocytopenia purpura (TTP). Although we believe this condition was due to the Mitomycin treatment that was completed one month earlier, this was reported to the IRB as a possible adverse event unlikely to be related to the vaccine. The patient was taken off study. The patient's condition improved, symptoms of TTP have resolved, and the patient remains in complete remission.

2.8 Phase II Study of Lethally Irradiated Allogeneic Pancreatic Tumor Cells Transfected with the GM-CSF Gene.

2.8.1 Preliminary Data

Sixty research participants received at least one and a maximum of five vaccinations of two pancreatic cancer cell lines each delivering 2.5×10^8 cells intradermally distributed among three lymph node regions in the Johns Hopkins study, IRB # 00-01-13-02 (SKCCC J9988) 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. See Table 2 for the demographic details. Vaccine one was administered 8-10 weeks following surgical resection. Patients were subsequently treated with 5-fluoruracil (5-FU) continuous infusion based chemotherapy integrated with radiotherapy. Research participants who remained disease-free one month after completing the chemoradiotherapy received the vaccines two through four one month apart. A fifth and final vaccine was administered six months after the fourth vaccine.

Table 2. Research Participants' Demographic Data

Characteristic	**N=60**
Male	37
Female	23
Median age	56.7
Age range	41-83
Node +	52
Margin +	18
Node + and Margin +	18

Enrollment was completed in January of 2005. At an early analysis, 56 patients were evaluable at one year and 36 patients were evaluable at two years. The one and two year survival rates are 88% and 76%, respectively. This data compares very favorably with the available published data.

2.8.2 Early Safety Data

Based on an early analysis if the data we conclude that the administration of the GM-CSF allogeneic cancer vaccine is safe and well tolerated. Treatment related side effects were similar to those side effects seen in the phase I study. The most common side effects were local responses of transient vaccine injection site reactions of induration and erythema in all research participants while some people had also transient vaccine injection site reactions of tenderness and pruritus. The systemic reactions included transient elevation in eosinophil counts, rashes and flu-like symptoms that have included low grade fever, chills, malaise, arthralgias, myalgias, and fatigue. Most patients have a transient elevation in their eosinophil count. All vaccine related toxicities have been on the same intensity and duration as those seen in the phase I study.

3.0 Study Design and Treatment Plan

3.1 Trial Overview

This vaccine boost trial will evaluate an equal mixture of two allogeneic GM-CSF secreting pancreatic vaccine cell lines Panc 10.05 and Panc 6.03 for: (1) safety of administration, (2) induction of antitumor immune responses, and (3) disease-free and overall survival in patients with resected adenocarcinoma of the head, neck, tail, or uncinate of the pancreas. Candidates for this study have either: 1) previously been treated at Johns Hopkins with the allogeneic GM-CSF secreting pancreatic cell lines Panc 10.05 and Panc 6.03 per protocol 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 protocol 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; or, 2) received other adjuvant chemoradiation and are now interested in participating in a vaccine study. All patients must meet the eligibility criteria including having no radiographic evidence of disease recurrence at the first vaccination and every semi-annual vaccination. As of Amendment #9, participants will be switched to annual vaccinations.

In this study research participants will receive 5×10^8 cells of a equal mixture of two allogeneic GM-CSF secreting pancreatic vaccine cell lines Panc 10.05 and Panc 6.03 divided into six intradermal injections every year until there is radiographic evidence of disease recurrence, toxicities occur, or the vaccine supply is exhausted. This is the same dose found to be safe and to induce immune responses in the phase I study, and has been shown to be safe in the follow-up of 60 patients in the phase II study. For research participants who had previously received the pancreatic cancer vaccine, one of the semi- annual vaccination boost dates will be the same as the annual follow-up date per protocol application number NA_00036444 (SKCCC J0248), entitled "Long term follow-up of patients who received lethally irradiated pancreatic tumor cells transfected with

the GM-CSF gene." Assessments and tests included in the long term follow-up will not be duplicated if included in this protocol.

3.2 Study Population

Patients with 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 uncinate of the pancreas and who have no radiographic evidence of pancreatic cancer disease recurrence may be eligible to participate in this study.

There will be two cohorts of research participants: those who have previously received the pancreatic cancer vaccine (no more than 17) and those who are vaccine naïve (30-45). At the time of the initial application of this study there appeared to be 18 research participants of previous pancreatic cancer vaccine studies who may have been eligible for this study. This includes three research participants from the Phase I study and 1 research participants who have completed the protocol-specified vaccines in the Phase II study. Also in this study we estimate enrolling between 30 and 45 research participants who are pancreatic cancer vaccine naïve. Both cohorts of research participants will need to be off all anti-cancer therapy for at least 28 days. It is estimated that we may need to consent up to 100 patients 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 the off-study visit (+/- 30 days). Since the off-study date from the parent vaccine study may have occurred more than one year ago, new semi-annual dates for vaccine boosting may be established. For research participants who are vaccine naïve, their first vaccine will be given at least 28 days after their last adjuvant anti-cancer therapy.

One of the semi-annual vaccine boost dates will be the same as their annual long term-follow-up visit date. Subsequent vaccine boosts will be administered 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. As of Amendment #9, participants will be switched to annual vaccinations (+/- 30 days). 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 later meet the eligibility criteria. There is no time limit. If eligibility is later established, semi-annual or annual dates for vaccine boosting and long term follow-up will be re-set as the date of the most recent vaccination.

In the event that a research participant has evidence of persistent vaccine-related responses (including, but not limited to: vaccine site flares such as recurrent erythema, induration, and pruritus at previous vaccine administration sites; urticaria) occurring at the frequency of more than once in the previous three months, the research participant may choose to delay the semi-annual or annual boost vaccination for up to one year after the last vaccine-related response. The research participant may also choose to continue to receive the semi-annual or annual boost vaccinations per protocol with evidence of persistent vaccine-related responses. Research participants experiencing urticaria must wait at least one month since the last hive before receiving another vaccine.

3.2.1 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 or 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 patient does not initially meet the eligibility requirements, the criterion that is not met may be re-evaluated within four weeks of the planned vaccination date without repeating all other screening criteria. In the event that eligibility is not met within four weeks of the planned vaccination date, all screening criteria must be re-evaluated.

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 or annual dates for vaccine boosting and long term follow-up will be re-set as the date of the most recent vaccination.

In the event that a priming or boost vaccination is not given as scheduled due to health issues (examples include but are not limited to infection or inflammatory process) or other reasons beyond the control of the research participant (examples include but are not limited to inclement weather and serious illness or death within the family) the vaccination may be delayed for up to three weeks. If an extension longer than three weeks is needed, the IRB will be consulted for a protocol exemption.

3.2.2 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 uncinate 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 surgery and any adjuvant therapy at least 28 days prior. Treatment administered in conjunction with surgery is at the discretion of the local oncologists. Options may include: neo-adjuvant chemotherapy, neo-adjuvant radiation, post-surgical adjuvant chemotherapy, post-surgical adjuvant radiation.

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 ≥ 9 gm/dl, ANC ≥ 1500 #/cu mm, platelets ≥100,000 K/cu mm)

7. Have adequate renal function (Serum creatinine ≤ 2 mg/dL).

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

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

3.2.3 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.

8. History of another cancer (other than pancreatic cancer) in the past five years except for treated non-melanoma skin cancer, superficial bladder cancer, or carcinoma-in-situ of the cervix.

3.2.4 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 12 months prior (+/- 30 days).

2. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

3. Have adequate hematologic function (Hemoglobin ≥ 9 gm/dl, ANC ≥ 1500,/cu mm, platelets ≥100,000/cu mm)

4. Have adequate renal function (Serum creatinine ≤ 2 mg/dl).

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

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

3.2.5 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 (except for short-term steroid therapy ending at least two days prior to vaccine administration).

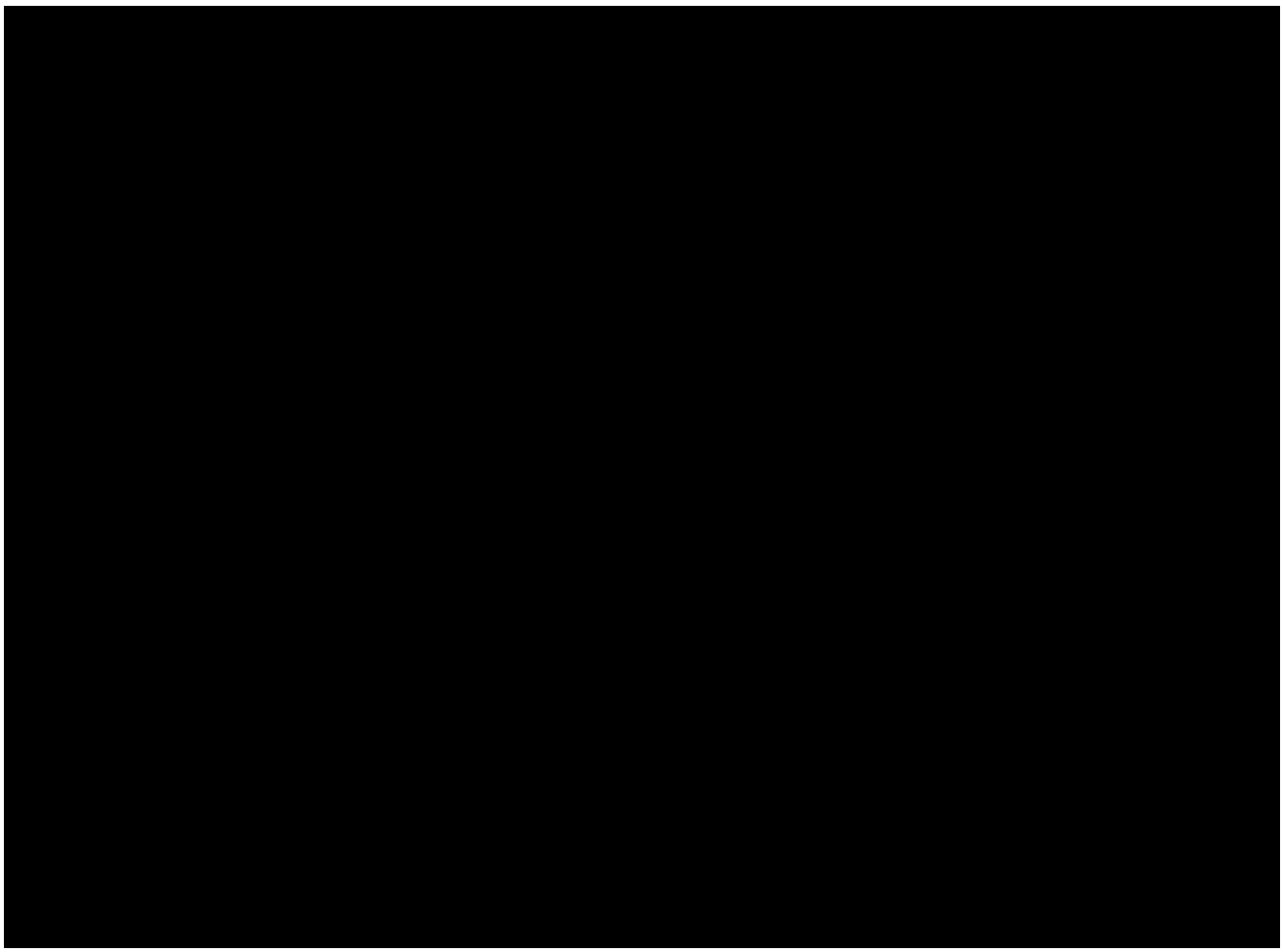
5. Anticipated need for systemic steroid therapy within 28 days after vaccine administration.

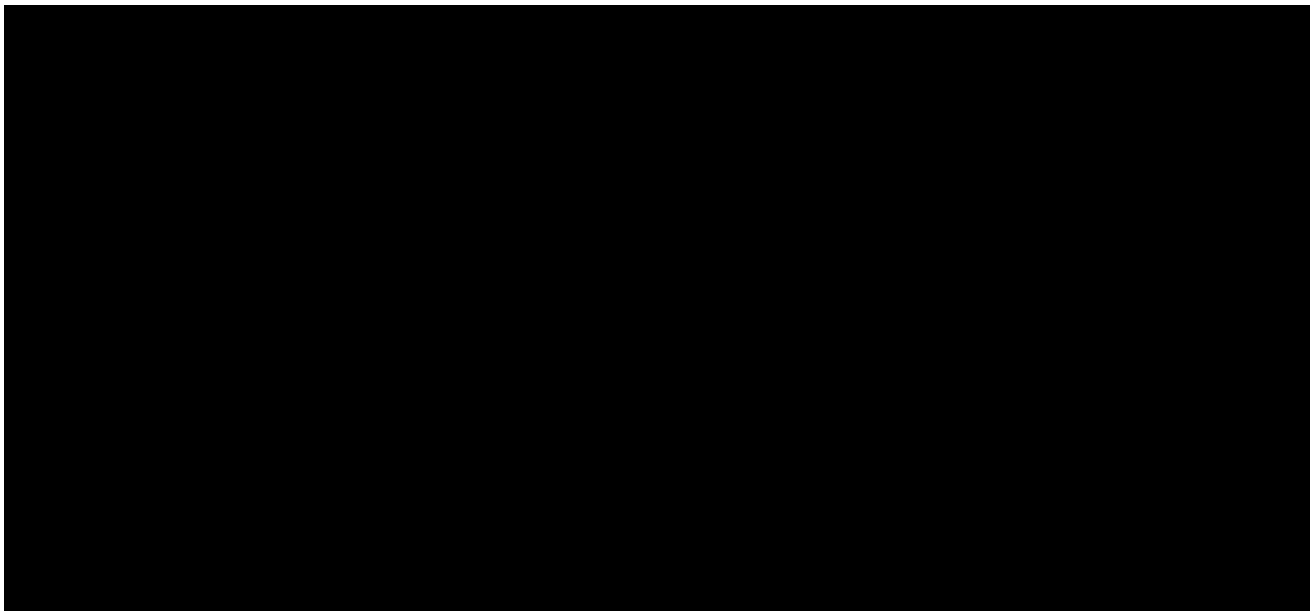
6. Evidence of active infections.

7. Pregnant.

3.3 Vaccine Production

[redacted]





[redacted]

[redacted]

Vaccine Administration

[redacted]

[redacted]

3.4 Study Plan

3.4.1 Schedule

The previously vaccinated cohort receives the vaccine boost once every six months (+/- 30 days). As of Amendment #9, participants will be switched to annual vaccinations (+/- 30 days).

The vaccine naïve cohort receives the priming vaccine once every month (+/- 3 days) for three months, then a vaccine boost every six months (+/-30 days) beginning six months after prime vaccine #3. As of Amendment #9, participants will be switched to annual vaccinations (+/- 30 days).

At any time during the study additional leukapheresis or approximately 200 cc of blood may be obtained, and skin biopsies and photos may be taken of the vaccine sites and rashes, as clinical indicated, as long as the research participant is in agreement.

All research participants will be seen in the oncology outpatient center for vaccine administration and monitoring. Research participants will be monitored for at least 30 minutes following vaccination for evidence of acute reaction to the injected vaccine cells.

Research participants and the study team may request additional optional study visits for discussions and evaluations. During these patient-requested or clinically-indicated visits, additional assessments may be obtained, including, but not limited to a history and physical examination, toxicity assessment, vital signs, skin biopsy, photos, imaging tests, and clinical laboratory testing.

3.4.1.1.Both Cohorts- Vaccination #1:

<u>This is the Prime Vaccination #1 for Vaccine Naïve Cohort and the Boost Vaccination #1 for Previously Vaccinated Cohort.</u>

Baseline data and samples (May be obtained from Day-28 to Day 0)

1. A clinical evaluation to include vital signs, ECOG status, weight, review of systems, physical examination, and toxicity evaluation.
2. CT scans of the abdomen, pelvis, and chest. If the CT scan is not done at Hopkins, the research participant must provide the report and a copy of the scans. If the research participant is allergic to the CT scan contrast or the contrast is contraindicated (as in the case for renal insufficiency), a non-contrast CT of the chest and a MRI of the abdomen and pelvis will be obtained.

3. A leukapheresis for in vitro studies will be encouraged. If the research participant refuses a leukapheresis, approximately 200 cc of blood will be drawn.
4. Blood testing to include CBC/diff, absolute eosinophils, absolute neutrophils, absolute lymphocytes, comprehensive chemistry panel including electrolytes, albumin, BUN, creatinine, AST, ALT, total bilirubin, alkaline phosphatase, amylase, and CA 19-9.
5. Research blood: 20 cc for serum banking.
6. 10 cc for HLA typing and 10 cc for EBV testing for vaccine naïve research participants only.
7. Skin biopsy for vaccine naïve research participants only.
8. Pregnancy test for women of childbearing potential. Urine pregnancy test preferred.
9. Several psychosocial and symptom instruments, including: quality of life, hope, trust and pancreatic cancer survivor surveys. (See appendices for copies of the instruments).
10. If not previously enrolled on IRB # NA_00036444 (SKCCC J0248) entitled, Long term follow-up of patients who received lethally irradiated allogeneic pancreatic tumor cells transfected with the GM-CSF gene, the research participant will be encouraged to join the long-term follow-up study.

Day 0

1. Administration of vaccine (Topical lidocaine-based anesthetic may be placed 1-2 hours prior to planned vaccine administration time to the intended vaccine sites.)
2. Day 0 serum GM-CSF level
3. Vital signs before and after vaccine administration
4. Photograph of vaccine sites (if clinically indicated)
5. Assessment for toxicities
6. Monitor for 30 minutes after vaccine administration
7. Tetanus toxoid boost if last tetanus vaccination > 10 years. Tetanus/diphtheria (Td) may be substituted if tetanus alone is not available. If both are not available, no tetanus vaccine will be administered.
8. Provide diary to record vaccine reactions, health/medical complaints and medication changes.

Day 1

1. Vital signs
2. Assessment of vaccine sites. This will include: number of sites that have erythema, induration, pruritus, and tenderness; and measurement of induration and erythema of largest vaccine site.
3. Assessment for toxicities
4. Day 1 serum GM-CSF level
5. Photograph of vaccine sites (if clinically indicated)

Day 2

1. Day 2 serum GM-CSF level

Day 3

1. Vital signs
2. Assessment of vaccine sites. This will include: number of sites that have erythema, induration, pruritus, and tenderness; and measurement of induration and erythema of largest vaccine site.
3. Assessment of toxicities

4. Day 3 serum GM-CSF level
5. Heme-8 with differential, including absolute eosinophil count. absolute neutrophils, absolute lymphocytes
6. Photograph of vaccine sites (if clinically indicated)
7. 3 mm punch skin biopsy of representative vaccine site (if clinically indicated)

Day 4

1. Day 4 serum GM-CSF level

3.4.1.2. Vaccine Naive Cohort Only:

Prime Vaccination #2 Day 0 is the same as Day 28 (+/- 3 days) after Prime Vaccination #1

Day 0

1. A leukapheresis for in vitro studies will be encouraged. If the research participant refuses a leukapheresis, approximately 200 cc of blood will be drawn.
2. Vital signs before and after vaccine administration
3. Assessment for toxicities and vaccine site reactions from previous vaccinations, and medications.
4. Administration of vaccine (Topical lidocaine-based anesthetic may be placed about 1-2 hours prior to planned vaccine administration time to the intended vaccine sites.)
5. Photograph of vaccine sites (if clinically indicated)
6. Assessment for toxicities.
7. Monitor for 30 minutes after vaccine administration.
8. Several psychosocial and symptom instruments, including: quality of life, hope, and trust surveys. (See appendices for copies of the instruments).
9. If not previously enrolled on IRB # NA_00036444 (SKCCC J0248) entitled, Long term follow-up of patients who received lethally irradiated allogeneic pancreatic tumor cells transfected with the GM-CSF gene, the research participant will be encouraged to join the long-term follow-up study.
10. Collect and review the diary of prime vaccine #1. Provide new diary.

3.4.1.3. Vaccine Naive Cohort Only:

Prime Vaccination #3 Day 0 is the same as Day 28 (+/- 3 days) after Prime Vaccination #2

Day 0

1. A leukapheresis for in vitro studies will be encouraged. If the research participant refuses a leukapheresis, approximately 200 cc of blood will be drawn.
2. Vital signs before and after vaccine administration
3. Assessment for toxicities and vaccine site reactions from previous vaccinations, and medications.
4. Administration of vaccine (Topical lidocaine-based anesthetic may be placed about 1-2 hours prior to planned vaccine administration time to the intended vaccine sites.)
5. Photograph of vaccine sites (if clinically indicated)
6. Assessment for toxicities

7. Monitor for 30 minutes after vaccine administration
8. Several psychosocial and symptom instruments, including: quality of life, hope, and trust surveys. (See appendices for copies of the instruments).
9. If not previously enrolled on IRB # NA_00036444 (SKCCC J0248) entitled, Long term follow-up of patients who received lethally irradiated allogeneic pancreatic tumor cells transfected with the GM-CSF gene, the research participant will be encouraged to join the long-term follow-up study.
10. Collect and review the diary of prime vaccine #2. Provide new diary.

Day 28 after Prime Vaccine #3 (-3 /+ 14 days)

1. A leukapheresis for in vitro studies will be encouraged. If the research participant refuses a leukapheresis, approximately 200 cc of blood will be drawn.
2. Vital signs.
3. Assessment for toxicities and vaccine site reactions from previous vaccinations, and medications.
4. Photograph of vaccine sites or reactions (if clinically indicated)
5. Several psychosocial and symptom instruments, including: quality of life, hope, and trust surveys. (See appendices for copies of the instruments).
6. If not previously enrolled on IRB # NA_00036444 (SKCCC J0248) entitled, Long term follow-up of patients who received lethally irradiated allogeneic pancreatic tumor cells transfected with the GM-CSF gene, the research participant will be encouraged to join the long-term follow-up study.
7. Collect and review the diary.

3.4.1.4. Both Cohorts- Semi-annual or Annual Boost Vaccinations after the previous vaccination:

In the event that a research participant has evidence of persistent vaccine-related responses (including, but not limited to: vaccine site flares such as recurrent erythema, induration, and pruritus at previous vaccine administration sites; urticaria) occurring at the frequency of more than once in the previous three months, the research participant may choose to delay the semi-annual or annual boost vaccination for up to one year after the last vaccine-related response. If the research participant chooses to delay the semi-annual or annual vaccinations due to persistent vaccine-related responses, evaluations to include: research and standard blood samples; clinical evaluation; CT scans of the abdomen, chest, and pelvis; and surveys, as described in "Day-28 to Day 0" below may be obtained semi-annually or annually.

The research participant may also choose to continue to receive the semi-annual or annual boost vaccinations per protocol with evidence of persistent vaccine-related responses. Research participants experiencing urticaria must wait at least one month since the last hive before receiving another vaccine.

Data and samples may be obtained from Day-28 to Day 0

1. A clinical evaluation to include vital signs, ECOG status, weight, review of systems, physical examination, and toxicity evaluation.

2. CT scans of the abdomen, pelvis, and chest. If the CT scan is not done at Hopkins, the research participant must provide the report and a copy of the scans. If the research participant is allergic to the CT scan contrast or is contraindicated, a non-contrast CT of the chest and a MRI of the abdomen and pelvis will be obtained.
3. A leukapheresis for in vitro studies will be encouraged. If the research participant refuses a leukapheresis, approximately 200 cc of blood will be drawn. As of Amendment #8, research bloods are no longer required to be collected.
4. Blood testing to include CBC/diff, absolute eosinophils, absolute neutrophils, absolute lymphocytes, comprehensive chemistry panel including electrolytes, albumin, BUN, creatinine, AST,ALT, total bilirubin, and alkaline phosphatase, amylase, and CA 19-9.
5. Research blood: 20 cc for serum banking. As of Amendment #8, research bloods are no longer required to be collected.
6. Pregnancy test for women of childbearing potential. Urine pregnancy test preferred.
7. If not previously enrolled on IRB # NA_00036444 (SKCCC J0248) entitled, Long term follow-up of patients who received lethally irradiated allogeneic pancreatic tumor cells transfected with the GM-CSF gene, the research participant will be encouraged to join the long-term follow-up study.

Day 0

1. Administration of vaccine (Topical lidocaine-based anesthetic may be placed about 1-2 hours prior to planned vaccine administration time to the intended vaccine sites.)
2. Vital signs before and after vaccine administration
3. Photograph of vaccine sites (if clinically indicated)
4. Assessment for toxicities
5. Monitor for 30 minutes after vaccine administration
6. Tetanus toxoid boost if last tetanus vaccination > 10 years. Tetanus/diphtheria (Td) may be substituted if tetanus alone is not available. If both are not available, no tetanus vaccine will be administered.

Day 28 after Boost Vaccine (-3/ + 14 days)

1. A leukapheresis for in vitro studies will be encouraged. If the research participant refuses a leukapheresis, approximately 200 cc of blood will be drawn. As of Amendment #8, research bloods are no longer required to be collected.
2. Assessment for toxicities and vaccine site reactions from previous vaccinations, and medications.
3. Photograph of vaccine sites or reactions (if clinically indicated)
4. If not previously enrolled on IRB # NA_00036444 (SKCCC J0248) entitled, Long term follow-up of patients who received lethally irradiated allogeneic pancreatic tumor cells transfected with the GM-CSF gene, the research participant will be encouraged to join the long-term follow-up study.

If the research participant is unable to return to Johns Hopkins for the day 28 after boost visit, effort will be made to obtain information for this visit. Data may be obtained regarding toxicity and vaccine site reactions by study clinician contact with the research participant, his/her family, or health care providers. The surveys may be mailed to the research participant's home with a stamped return envelope. Fax and electronic correspondence for the diaries and surveys is also

acceptable. Arrangements may be made for the research samples to be obtained locally and shipped to the Hopkins' Jaffee Lab.

Off-study

1. A clinical evaluation to include vital signs, ECOG status, weight, review of systems, physical examination, measurement of vaccine sites and toxicity evaluation.
2. CT scans of the abdomen, pelvis, and chest. If the CT scan is not done at Hopkins, the research participant must provide the report and a copy of the scans. If the research participant is allergic to the CT scan contrast or the contrast is contraindicated (as in the case for renal insufficiency), a non-contrast CT of the chest and a MRI of the abdomen and pelvis will be obtained.
3. A leukapheresis or approximately 200 cc of peripheral blood will be obtained for in vitro studies. As of Amendment #8, research bloods are no longer required to be collected.
4. Research blood: 20 cc for serum banking. As of Amendment #8, research bloods are no longer required to be collected.
5. Blood testing to include CBC/diff, absolute eosinophils, absolute neutrophils, absolute lymphocytes, comprehensive chemistry panel including electrolytes, albumin, BUN, creatinine, AST, ALT, total bilirubin, alkaline phosphatase, and CA 19-9.
6. Assessment of vaccine sites. This will include: number of sites that have erythema, induration, pruritus, and tenderness; and measurement of induration and erythema of largest vaccine site.
7. Assessment of toxicities (Information may include evaluations made by the local health care provider.)

If the research participant is unable to return to Johns Hopkins for the off-study visit, effort will be made to obtain medical records that may include laboratory and imaging tests results, pathology reports, and health care providers' notes. Data may also be obtained regarding toxicity and disease status by study clinician contact with the research participant, his/her family, or health care providers. The surveys may be mailed to the research participant's home with a stamped return envelope. Fax and electronic correspondence for the diaries and surveys is also acceptable. Arrangements may be made for the research samples to be obtained locally and shipped to the Hopkins' Jaffee Lab.

If the off-study visit is within 28 days of a protocol-specified visit in which the assessments and samples were obtained, the off-study assessments and specimens need not, but may be, repeated.

Research Samples

De-identified samples may be shared with other investigators with written authorization from the principal investigator. Additional samples may be collected for research purposes, including, but not limited to those obtained through biopsies, surgeries, and autopsies. As of Amendment #8, research bloods are no longer required to be collected.

Table 3. Study schema including toxicity and immune monitoring for Prime Vaccine #1 and each Boost Vaccination.

Assessment	Day 0[1]	Day 1	Day 2	Day 3	Day 4				Day 28[2]
Clinical evaluation	X								
CT abd/chest/pelvis	X								
Vital signs[3]	X	X[4]		X[4]					X[10]
Toxicity assessment/evaluation[5]	X	X[4]		X[4]					X[5,6,]
Vax site assessment[5]		X[4]		X[4,6]					X[5,6]
Heme/ diff/abs.eos	X								
Chemistries[7]	X								
CA 19-9	X								
Amylase	X								
Leukapheresis or PBL *in vitro* studies [8]	X								X
Research blood: HLA typing and EBV testing[9]	X								
Research blood: Serum banking[8]	X								
Vaccine site biopsy[8]	X[9]								
Photograph, if indicated[9]	X	X[6]		X[6]					X[6]

[1] May be done up to 28 days prior to Day 0. Additional leukapheresis may be performed for an interesting immunological response.
[2] Day 28 (-3/ +14 days) assessments and samplings are to be done after each vaccination.
[3] Vital signs include temperature, pulse rate, respiration rate, and blood pressure
[4] At first vaccination only.
[5] Assess to resolution.
[6] Information may be obtained by phone, e-mail, fax, and/or through the evaluation by the local health care provider, if unable to assess in person.
[7] Chemistries include: electrolytes, albumin, BUN, creatinine, AST, ALT, total bilirubin, and alkaline phosphatase
[8] At any time 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. As of Amendment #8, research bloods are no longer required to be collected.
[9] Obtain baseline biopsy, HLA typing and EBV testing prior to the first vaccine only for the vaccine naïve cohort only.
[10] Prime vaccine 3 only.

The significant results of all assessments indicated above in Table 3 will be recorded in an electronic database.

3.4.2 Leukapheresis

All research participants will be encouraged to periodically undergo a leukapheresis as outlines in the protocol. If the research participant does not agree to the leukapheresis the standard 200 cc of peripheral blood will be obtained. In addition, any research participant demonstrating an interesting immunological response may be asked to undergo leukapheresis to obtain greater numbers of lymphocytes for research purposes. This may include physical responses thought to be related to the vaccine (including, but not limited to vaccine site flares) or interesting laboratory responses (including, but not limited to mesothelin-specific CD8+T cell responses). There will be at least two weeks between additional leukapheresis procedures. As of Amendment #8, research bloods are no longer required to be collected.

Prior to the leukapheresis, subjects will be evaluated by the Hematopoietic and Therapeutic Support (HATS) Center to determine if their vascular access appears to be adequate for the leukapheresis procedure.

If the research participant had a leukapheresis within two weeks (+/- 14 days) of a protocol-specified research sample collection point, the peripheral blood lymphocyte collection of 200 cc of blood and the peripheral blood lymphocyte collection need not be repeated.

3.4.3 Evaluation for Safety and Anticipated Toxicities

Severe toxicities are unlikely, based on information from previous GM-CSF gene vaccine studies completed here at Johns Hopkins Hospital trials, including the Phase I and II pancreatic tumor vaccine trials. In experiments involving over 400 mice, use of irradiated GM-CSF secreting tumor cells caused only reversible lymphadenopathy and reversible subcutaneous swelling; no ulcerations were seen. In our first phase I trial in patients with renal cell carcinoma, only local erythema and swelling were seen following intradermal injections of cell doses up to 4×10^7 GM-CSF modified vaccine cells, and up to 4×10^8 unmodified vaccine cells.

At the highest dose level, we predict that initially 45 mcg of total GM-CSF will be secreted locally per 24 hours, a level that will diminish as tumor cells are killed by invading inflammatory cells. To support hematologic recovery in oncology patients after intensive chemotherapy, subcutaneous or intravenous doses of GM-CSF between 5 and 10 ug/kg/day are commonly used (350-700 mcg total for a 70 kg individual). At this dose range the following side effects are commonly seen: local or generalized skin rashes, bone pain (attributed to stimulation of hematopoietic progenitors), fever, and malaise. Although patients in the initial Phase I study of the allogeneic tumor vaccine had normal bone marrow function, leukocytosis and toxic levels of serum GM-CSF did not occur with the 10 fold lower dose of GM-CSF. The maximum serum GM-CSF level obtained was 14.0 pg/ml with dose level four at 48 hours after the first pancreatic tumor vaccine.

The plasmid used to transfect the GM-CSF gene is safe. In contrast to retroviral vectors, it lacks the coding sequences that would allow replication and the generation of helper virus. This plasmid containing the GM-CSF gene has been sequenced following vector construction to confirm its insertion, orientation, and the lack of mutations. In addition, this vector has been confirmed to produce bioactive GM-CSF.

The risk of generating autoimmune reactions is unknown but is believed to be small. The pancreas would be the most likely organ to be involved. Pancreatitis and loss of pancreatic function can be supported by the use of exogenous pancreatic enzymes and insulin injections if needed. Other organs that may share tissue specific antigens might also be involved, such as the salivary glands and other gastrointestinal organs. In the Phase I and II studies there were no evidence of autoimmune reactions.

Every patient who has received the vaccine will be evaluated for toxicity. The research participant will be taken off-study if unacceptable adverse events are experienced. Possible toxicities include local swelling, induration, or ulceration at the site of the vaccine, systemic toxicities from paracrine secretion of GM-CSF, and induction of autoimmunity. Patients will be evaluated on days 1 and 3 by a research nurse following the semi-annual or annual vaccination boosting to monitor for local and systemic toxicities. The research participant may be contacted by phone or e-mail or the information may be obtained from their local health care providers. The research participant will be advised to call the research nurse and/or the principal investigator if there are any new toxicities, concerns or questions.

3.4.4 Interval Health Care

The research participant disease status may be evaluated more frequently than twice a year. Patients may undergo additional abdomen, chest and pelvis CT scans and blood tests, including CA 19-9 levels, as recommended by their local oncology, or by the study team as standard of care for possible disease recurrence. The results of the CT scans, blood tests, and progress notes will be requested from the research participant's local oncologist. Medical records obtained will be added to the oncology outpatient medical records, including electronic forms, when possible. Data related to the toxicity and/or disease status assessments will be recorded in the case report form binders and electronic data base.

If the research participant is followed at Johns Hopkins, the medical records will be accessed at least quarterly, and more frequently, if needed for disease recurrence.

If patient is taken off study, the patient's medical records will be requested from the health care provider providing further care for 28 days after the last research product was administered, or longer for resolution of any adverse events related to the research product. After off-study, the research participant will be followed annually via the protocol application number NA_00036444, entitled, "Long-term follow-up of patients who receive lethally irradiated allogeneic pancreatic tumor cells transfected with the GM-CSF gene", SKCCC J0248, if consent is granted.

3.4.5 Continuation of Therapy

Provided there is no radiographic evidence of pancreatic cancer disease recurrence, no dose limiting toxicities, and the vaccine is available, the patient will receive an equal mixture of allogeneic pancreatic cancer cell lines Panc 10.05 and Panc 6.03 for a total dose of 5×10^8 vaccine cells divided equally into six intradermal injections to be given as two in each anterior upper thigh and two in the non-dominant upper arm (unless contraindicated) twice every year.

In the event that a research participant has evidence of persistent vaccine-related responses (including, but not limited to: vaccine site flares such as recurrent erythema, induration, and pruritus at previous vaccine administration sites; urticaria) occurring at the frequency of more than once in the previous three months, the research participant may choose to delay the semi-annual or annual boost vaccination for up to one year after the last vaccine-related response. The research participant may also choose to continue to receive the semi-annual or annual boost vaccinations per protocol with evidence of persistent vaccine-related responses. Research participants experiencing urticaria must wait at least one month since the last hive before receiving another vaccine.

The same study schema (Table 3.) that includes toxicity and immune monitoring will be followed with each semi-annual or annual vaccination.

3.4.6 Off-study

Research participants will be discontinued from participating in this study for the following circumstances:

- There is radiographic evidence of pancreatic cancer recurrence.
- Serious vaccine related adverse events occur.
- The vaccine supply is exhausted.
- The research participant is noncompliant, is unable to comply with the treatment plan, or requests withdrawal.
- The research participant is receiving concomitant immunotherapy, chemotherapy, radiotherapy, or other biological or gene therapy.

If determined to be off-study, the research participant will be followed for 28 days after the administration of the last vaccine for toxicities related to the vaccine, or longer, if vaccine-related toxicities occur. Whenever possible, the research participant will be asked to have the tests indicated for the day 28 visit as the off-study visit, unless this was done within 28 days of the off-study date.

If the research participant consents there will be a lifelong follow-up through participation in Dr. Daniel Laheru's study, IRB # NA_00036444 (SKCCC J0248) entitled, Long term follow-up of patients who received lethally irradiated allogeneic pancreatic tumor cells transfected with the GM-CSF gene.

3.5 Management of Toxicities

Local vaccine site reaction may be treated with topical applications of aloe vera or vitamin E gel or lotion. Significant local inflammation that is causing the research participant severe pain or is interfering with the activities of daily living may be treated with cold packs and oral analgesics. Local toxicities of pruritus at the vaccine sites and systemic pruritus may be treated with topical or oral diphenhydramine hydrochloride (Benadryl) or topical aloe vera. If oral diphenhydramine hydrochloride is used the recommended dose shall be 25-50 mg every four to six hours as needed for pruritus, not to exceed 300 mg/day. Cases of local ulceration should be manageable with local

wound care, with or without antibiotics. Severe local inflammation or significant clinical autoimmunity will be managed on a case by case basis.

4.0 Statistical Considerations

4.1 Sample Size

The primary statistical endpoint of this study is to evaluate the safety and feasibility of vaccine boosting with lethally irradiated allogeneic pancreatic tumor cells transfected with the GM-CSF gene. Among patients who have previously been treated with the vaccine, the cohort is limited to those who continue to have no disease recurrence for at least 1 year after treatment. Currently, there are three potentially eligible patients from the original phase I study, and 14 from the phase II study. A total of up to 17 previously treated patients will be eligible to continue to receive vaccine treatment in the form of semi-annual boosts. The second cohort of vaccine naïve patients who have been recurrence free for at least 28 days following adjuvant therapy will be given three priming vaccines each a month apart, followed by semi-annual vaccine boosts in order to determine the feasibility of administering the vaccination to vaccine naïve patients and to obtain initial estimates of the efficacy of such treatment with respect to prolonging disease-free status. As of Amendment #9, participants will be switched to annual vaccinations. We will base our determination of feasibility by estimating the proportion of patients with a dose limiting toxicity (DLT) within 28 days of the first vaccine treatment. Between 20 and 45 vaccine naïve patients will be included. An initial group of 20 patients will be recruited and an interim analysis will be performed in order to guard against excessive toxicities relating to treatment. No DLTs have been observed in neither the phase I or II studies. If there is significant evidence that more than 10% of the vaccine naïve patients have dose limiting toxicities within 28 days of the first vaccination, then the trial will be halted. If 6 out of 20 of the initial patients have DLTs, the lower bound of the exact 95% confidence interval for the proportion of patients with a DLT is 11.89%. Therefore, we will halt the trial due to excessive toxicity at the interim analysis if 6 or more patients have a DLT within the first 28 days of their first vaccine. Otherwise, an additional 20 vaccine naïve patients will be accrued. If 20 patients are accrued, the maximum width of the 95% confidence interval estimate of the proportion of patients with a DLT is 0.438. If the full cohort of 40 patients is accrued, then the maximum width of the 95% confidence interval is 0.309.

The sample size was expanded to include a cohort of up to 45 vaccine-naïve research participants and 17 previously vaccinated research participants for a total sample up to 62 research participants.

4.2 Analysis of Primary Endpoint: Safety and toxicity measurements

The primary endpoint of this study is safety as measured by local and systemic toxicity. These toxicities will be characterized according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0, and can be accessed and downloaded via the website: http://ctep.cancer.gov/reporting. Dermatologic toxicity measurements of the vaccine sites will be performed. For each patient cohort (vaccine naïve and vaccine treated), we will tabulate the number, type and degree of toxicities for each round of vaccination. In addition, we will estimate the proportion of individuals who have a DLT within the first 28 days of vaccination for each round with an exact 95% confidence interval.

4.3 Analysis of Secondary Endpoints

The analysis of the remaining endpoints are primarily descriptive in nature and are intended to be used to generate estimates of efficacy and hypotheses to be tested in later trials. For each endpoint, separate analyses will be performed for the vaccine naïve and vaccine treated patients.

4.3.1 Efficacy endpoints

The primary efficacy endpoint of interest is the overall survival (OS) of patients treated with vaccine boosts. The overall survival is defined as the time from the first vaccine boost until death. If a patient is lost to follow-up or the study is ended prior to death, the patient will be considered censored at their last recorded follow-up. For each cohort, Kaplan Meier curves will be constructed and the median survival estimates will be calculated with 95% confidence intervals using Greenwood's formula. Since the time between completion of treatment and the initiation of vaccine boosts will vary among subjects, we will use a Cox proportional hazards model to adjust for this delay in boosts.

We are also interested in investigating the effect of vaccine boosts on recurrence free survival (PFS). Patients who are treated at Johns Hopkins will be followed every 3 months and evaluated for recurrence. However, the standard of care follow-up varies from institution to institution. In order to prevent biasing our results, it is necessary to coarsen the follow-up interval so that every individual is evaluated at the same time points regardless of the institution. For example, if the only visits held in common among all patients were the semi-annual exams prior to vaccine boosting, it would be necessary to only consider the status of the JH patients at those two time points regardless of recurrence information gained from the additional 2 visits. This coarsening of the data may cause an overestimation of PFS. In order to take into account both potential forms of bias, we will perform our analysis of PFS on the entire cohort as well as the subpopulation of patients from Johns Hopkins (estimated to be approximately 50% of the research participants). PFS will be defined as the time from the first vaccine until evidence of disease recurrence. If a patient withdraws from the study prior to being diagnosed with progressive disease, they will be censored at the date of their last follow-up visit. If an individual dies prior to being diagnosed with progressive disease, they will be considered to have progressed at the date of their last follow-up visit. This is a conservative estimate if we count the disease recurrence at the next planned visit then this will bias the PFS time upward. The PFS will be summarized using Kaplan-Meier curves and estimates of median PFS with 95% confidence intervals based upon Greenwood's formula. Due to potential causes of bias discussed earlier, the results will be considered extremely preliminary. If the PFS estimates for patients treated at Johns Hopkins appear to be lower than that of the population as a whole and the Johns Hopkins patients are followed at more frequent intervals than the other patients, then this indicate that an overestimation of PFS may exist. No formal comparison is planned due to the small sample size. Such results could affect the future planning of follow-up treatment for patients in subsequent trials.

Measurements of immune response include but are not limited to mesothelin, prostate stem cell antigen (PSCA) and mutated k-ras-specific T cell responses. Continuous variables will be summarized with means and standard deviations. Dichotomous and categorical variables will be

summarized using proportions with exact 95% confidence intervals and counts, respectively. These summaries will be computed for each patient at two time points around each vaccine boost: pre-vaccination and four weeks post vaccination. Plot will be used to show the changes in immune response over time both for each individual and for each cohort. For each vaccine boost, comparisons in the pre and post-vaccine responses will be compared using paired t-tests (or Wilxcoxon signed rank tests if appropriate) for continuous variables and Fisher's exact test for dichotomous or categorical variables. Associations between immune responses will be explored graphically (e.g. scatterplots, boxplots) and numerically (e.g. correlations, χ^2 tests).

Measurements of antitumor immunity include but are not limited to the measurement of shared tumor-specific antigens and k-ras specific antitumor immune responses. Autologous lymphocytes will be obtained from peripheral blood before each vaccination, and at four weeks following each vaccinations. The graphical and numerical analyses of these results will be the same as that described for measurements of immune responses and will be carried out for each cohort separately.

4.3.2 Relating immune response to clinical response

The relationships between immune and clinical responses will be assessed using a variety of statistical techniques. Preliminary explorations will be graphical in nature (e.g. boxplots, scatterplots). Univariate and multivariate modeling will be used quantify the associations. In the case of a binary clinical outcome (e.g. toxicity), logistic regression will be used. In the case of a time-to-event clinical outcome (e.g. OS), the Cox proportional hazards model will be used.

4.3.3 Longevity of an allogeneic vaccine

Pharmacokinetic studies will be used to evaluate the longevity of the allogeneic vaccine by measuring the levels of GM-CSF in the serum. Serum will be obtained from each research participant on days 0 and 3 of treatment. Pharmacokinetic parameters will be estimated, when possible, using standard compartmental models. Parameter estimates and normal theory standard errors will be calculated by fitting using weighted least squares. Summary statistics (e.g. mean, standard deviation) will be presented for each cohort on each day at each vaccine boost. Plots of the means against time will be included to assess the change in the parameters over time. The relationship between pharmacokinetic parameters and clinical outcomes will be assessed using logistic regression for binary outcomes (e.g. toxicity) and Cox proportional hazards models for time to event outcomes (e.g. OS, PFS).

4.3.4 Psychosocial and symptom profiles

The psychosocial and symptom profiles will be evaluated through the use of a variety of surveys and measurement tools. Surveys will be administered at several time points: day 0 and day 28 of the each vaccination. The responses will be measured using 8 techniques described in Section 5.3 and include topics such as concept of hope, symptom burden, patient satisfaction, and QOL. Categorical measurements such as those based upon Likert scales (e.g. Hearth Hope Index) will be summarized using counts, medians, ranges and estimates of the probability distributions. Continuous variables will be summarized using means and standard deviations. Trends over time

will be summarized by plotting the median measurements against time with an estimate of variability (e.g. standard deviation, inter-quartile range) for each cohort. Associations between measurements will be evaluated graphically (e.g. boxplots, scatterplots) and numerically (e.g. Spearman's correlation). Comparisons between time points will be made using non-parametric techniques (e.g. Kruskal-Wallis test, χ^2 test).

5.0 Response Criteria

5.1 Evaluation of Clinical Activity

Most patients will have only minimal residual disease at the time of enrollment. Therefore, there will be no evaluable disease to measure at baseline. Patients will be monitored for disease-free and overall survival. The results from this trial will be compared to historical controls seen at the Johns Hopkins Hospital (5). Patients recently seen at the Johns Hopkins Hospital who can be matched for pathologic stage, surgical intervention, and adjuvant combination chemotherapy and radiation therapy, are the most accurate group of historical controls since our institution has the largest reported experience treating patients with this disease and has recently reported the best survival statistics for current interventions (5).

Patients may undergo standard of care evaluations consisting of abdominal, chest, and pelvis CT scans at regular intervals to evaluate for local recurrence and distant metastases. In addition, any patient presenting with symptoms will undergo evaluation for metastases. Recurrent disease is defined as evidence of either local or metastatic recurrence by CT scan.

The serum tumor marker CA19-9 lacks a sufficient sensitivity and specificity to serve as reliable indicators of response. The CA 19-9 levels will be followed to evaluate whether large and persistent changes might correlate with either in vitro immune responses or with time to clinical recurrence.

5.2 Evaluation of Immune Responses

A central goal of the clinical trial is to identify immunologic changes associated with the vaccine therapy that may be markers of potential clinical responses. The local immune response to vaccine will be tested with biopsy and histological analysis. Specific systemic responses to tumor and to normal tissue will be assessed by in vitro assays.

The leukapheresis product or peripheral blood will be obtained from each research participant at periodic protocol-specified intervals for the in vitro assays. In addition, research participants may be asked to donate additional lymphocytes by leukapheresis. Informed consent will be obtained for this procedure using the Leukapheresis Informed Consent Form which is a separate document than the main vaccine study informed consent form.

De-identified samples may be shared with other investigators with written authorization from the principal investigator. Additional samples may be collected for research purposes, including, but not limited to those obtained through biopsies, surgeries, and autopsies.

5.2.1 In vitro analysis of induction of antitumor immunity

Autologous lymphocytes will be obtained from peripheral blood before the first and each semi-annual vaccination for in vitro immune monitoring studies. Approximately 200 ml of blood will be required at these time points for all of the following immunologic studies. Studies include the analysis of pancreatic adenocarcinomas for: (1) shared tumor-specific antigens, (2) k-ras specific antitumor immune responses. Twenty ml of blood will be obtained prior to each vaccination for serum banking.

5.2.2 Biopsy of Vaccine Site

Patients will be observed for signs of local inflammation and induration. If responses in this trial are similar to the responses observed in the Phase I and II allogeneic pancreatic tumor vaccine studies, marked inflammatory responses will be present between days 1 and 3. A baseline 3 mm punch biopsy will be obtained for vaccine naïve research participants only. Additional skin biopsies may be obtained, if clinically indicated. Vaccine sites may be photographed before injections and before biopsies. The biopsy sites will be anesthetized with local 1% lidocaine with 1:100,000 epinephrine.

Half of the biopsy specimen will be formalin fixed for hematoxylin and eosin stains. The other half of each biopsy specimen will be snap frozen in OCT for immunohistochemistry stains including; T cell staining (antiCD3), macrophage staining (Ham56), dendritic cell staining (S100), B cell staining (antiCD20), and cytokeratin staining (for presence of tumor cells).

To semiquantitate the immune infiltration, the slides will be interpreted without knowledge of the research participant's information. The type of immune cells infiltrating the vaccine site adjacent to the vaccine cells will be determined using the immunohistochemical stained slides. In addition, a semiquantitative estimate of the proportion of each infiltrating cell type will be determined using a grid to count the number of each cell type per number of tumor cells in that field. These methods for semiquantitation have been successfully employed in the renal vaccine trial. These results will be compared with the biopsy results from our previous vaccine trials.

The biopsy of the vaccine site should not significantly jeopardize any potential therapeutic benefit for the patient. The amount of vaccine and the number of responding immune cells removed by this biopsy is believed to be small.

5.3 Evaluation of psychosocial and symptom responses

There is a gap in the literature regarding the psychosocial and symptom profiles of long-term cancer survivors. For a cancer, such as pancreatic cancer, that has a dismal prognosis, the information gained through intermittent evaluations of research participants' quality of life, trust, hope, social support, decisional control preferences, advance directive preferences, and symptoms will be quite valuable. Due to limited research, the data collected through this study may bring forth new insights into the quality of life of people who are out living their expected survival time.

The surveys and measurement tools will be completed at days 0 and 28 while the research participant is physically at Johns Hopkins, if possible. On day 0, the goal is to have the forms completed prior to vaccination, but in order to minimize subject burden the forms may be completed during the monitoring period immediately after vaccination. If the participant has a visit scheduled at Hopkins, the day 28 surveys will be completed during the visit. If the participant is unable to complete the surveys during the day 0 or 28 visit they will be asked to return the surveys when completed. A stamped return addressed envelope will be provided if the participant is unable to complete the surveys at the visit, and a deviation from the standard timing will be noted.
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

The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 version 3 is a likert-scale evaluation of 30 items that focuses on physical activities, symptoms, overall health and overall quality of life.
The Quality of Life Scale: Patient/Cancer Survivor (QOL-CS) Version measures the quality of life (QOL) in people with cancer through a 41 item interval level scale. This QOL instrument has been used extensively in cancer survivorship research studies. It measures an overall QOL that has a Cronbach's alpha coefficient of 0.93, as well as four domains contained within QOL: physical, psychological, social, and spiritual well-being with subscale alphas of 0.71, 0.77, 0.81, and 0.89, respectively (Ferrell, Hassey-Dow & Grant, 1995, Ferrell, Hassey-Dow, Leigh, Ly, & Gulasekaram, 1995).
The Herth Hope Index is a four-point Likert scale with 12 items related to the concept of hope in this instrument developed by Herth (1991, 1992) that provides a score of 12 to 48, with a higher value indicating a higher level of hope.

The Symptom Distress Scale is a symptom burden assessment instrument developed by McCorkle and Young (1978) that measures the frequency and intensity of nausea and pain (2 items for each symptom), and a single measure of appetite, insomnia, fatigue, bowel, concentration, appearance, breathing, outlook, and cough on a five point Likert- like scale

The Patient Trust Scale is a 10 item survey strongly related to patient satisfaction and medical care ($r = 0.68$, $P < 0.0001$). It covers three dimensions: honesty, confidentiality, competency, and agency (Kao, Green, Zaslavsky, Koplna, & Cleary, 1998).

The Pancreatic Cancer Survivor Survey Research Participant Baseline Survey is being pilot tested in this clinical research study. The survey questions research participants on issues not covered in the previous established measurement tools, such as: research participation decision making, conflict of interest, informed consent, and advance directives.

6.0 Adverse and Problem Event Reporting

6.1. Responsibilities

It is the responsibility of the principal investigator to notify the IND sponsor of the vaccine research product, Elizabeth Jaffee, M.D., Hopkins Medicine Institutional Review Board, and Hopkins Institutional Biosafety Committee of any serious adverse event due to any cause, which occurs during the course of this investigation, and is believed to be in any way related to study drug. The sponsor will notify the appropriate federal regulatory agencies, including but not limited to the Food and Drug Administration.

The Principal Investigator or their designee must notify the IND sponsor, Elizabeth Jaffee, M.D. of any Serious Adverse Event (SAE) within 24 hours of the investigator learning that the adverse event has occurred. Events must be documented on the appropriate Johns Hopkins Medicine IRB form available at [redacted] See section 6.3 for IRB reporting guidelines.

All adverse and problem events occurring from day 0 to 28 of each vaccine cycle will be recorded. All serious adverse and problem events occurring from day 0 and 28 of each vaccine cycle will be reported to the IRB. All serious adverse events related to the vaccine and deaths will be recorded and reported to the IRB. Adverse events related to the vaccine will be followed to resolution.

Events of interest, including but not limited to, vaccine site flares and urticaria, may occur beyond 28 days after the vaccine administration. Immunologic events, such as vaccine site flares and urticaria will be recorded regardless of when they occur. These immunologic events are not to be considered adverse events, since these reactions may represent desired effects from the research product. There are no time restrictions on recording these events, as these events have been known to happen a long time after vaccination.

A *serious adverse event (SAE)* is one that:

- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolongation of an existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect in the offspring of an exposed patient

An important medical event that may not result in death, be life-threatening, or require hospitalization, may be considered a serious adverse drug experience when, based upon appropriate medical judgment, it jeopardizes the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

A *life threatening adverse event* is defined as any adverse experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

An *adverse drug reaction (ADR)* is a noxious and unintended response to a medicinal product in which a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. that the relationship cannot be ruled out.

6.2. Recording of an Adverse Event

The principal investigator is responsible for evaluating all adverse events, obtaining supporting documents, and determining that documentation of the event is adequate. The principal investigator is responsible for determining the severity and relationship of the adverse event to the investigational drug. The principal investigator may delegate these duties to sub-investigators and must assure that these sub-investigators are qualified to perform these duties under the supervision of the principal investigator.

All adverse events will be recorded in the subject's Case Report Form and in the study data base. The detailed description of the event will include appropriately graded severity of the adverse event and its relationship to the study drug.

Severity will be categorized by toxicity grade according to the NCI Common Terminology Criteria for Adverse Events version 3.0 available at http://ctep.cancer.gov/reporting/ctc.html

Adverse events not listed in the NCI Common Terminology Criteria for Adverse Events will be evaluated using the following criteria:

- Grade 1, Mild: Awareness of symptom, but easily tolerated; usually transient requiring no special treatment; does not interfere with usual status or activities
- Grade 2, Moderate*:* May be ameliorated by simple therapeutic measures; may interfere with usual activities
- Grade 3, Severe*:* Incapacitating, inability to perform usual activities
- Grade 4, Life-threatening/Disabling*:* Subject was at risk of death or significant disability at the time of the event
- Grade 5, Death related to AE

Relationship of the adverse event to the investigational drug will be determined by the principal investigator, and will be categorized as:

- ***Unrelated:*** The adverse event is clearly related to other factors such as the subject's clinical state, environmental factors, or other modes of therapy or concomitant drugs administered to the subject.
- ***Unlikely to be related:*** The adverse event may be related to other factors such as the subject's clinical state, environmental factors, or other modes of therapy or concomitant drugs administered to the subject.
- ***Possibly related:*** The adverse event follows a reasonable temporal sequence from administration of the study drug, and/or follows a known response pattern to the study drug, but could readily have been produced by the subject's clinical state, environmental factors, or other modes of therapy or concomitant drugs administered to the subject.
- ***Probably related:*** The adverse event follows a reasonable temporal sequence from administration of the study drug and follows a known response pattern to the study drug,

and cannot readily have been produced by the subject's clinical state, environmental factors, or other modes of therapy or concomitant drugs administered to the subject.

- ***Definitely related:*** The adverse event follows a reasonable temporal sequence from administration of the study drug and is clearly a known response pattern to the study drug, and cannot readily have been produced by the subject's clinical state, environmental factors, or other modes of therapy or concomitant drugs administered to the subject.

All grade 3 and 4 clinical laboratory results that represent an increase in severity from baseline will be reported as adverse events. A grade 1 or 2 clinical laboratory abnormality should be reported as an adverse event only if it is considered clinically significant by the investigator.

In the event of death, the cause of death should be recorded as the adverse event. An attempt will be made to obtain a copy of the death certificate. Because the long-term effects of gene therapy are not known, the National Institutes of Health (NIH) would like an autopsy, in the event of death. If an autopsy is performed, a copy of the autopsy report should be obtained.

6.3. Reporting Guidelines

We will use the current JHM IRB and FDA guidelines for reporting relevant problems, events, adverse events, and adverse drug reactions.

7.0 Clinical Trial Monitoring

This is a Level II study under the Sidney Kimmel Comprehensive Cancer Center (SKCCC) Data Safety Monitoring Plan. Data monitoring of this protocol will occur on a regular basis with the frequency dependent on the rate of subject accrual and the progress of the study. On a regular basis, the protocol will be internally monitored by the principal investigator, Daniel Laheru, M.D. and the study's sponsor, Dr. Elizabeth Jaffee. External data monitoring will be performed by the SKCCC Clinical Research Office Quality Assurance Program (CRO QA). The Data and Safety Monitoring Oversight will be conducted by the SKCCC Data and Safety Monitoring Committee (DSMC). The oversight will require no additional reporting from the study staff. Per the SKCCC at Johns Hopkins Data and Safety Monitoring Plan, revised on June 16, 2005, the CRO QA Program forwards their monitoring and auditing reports to the DSMC for review (section 2.1.6., 2.2.5.4., and 2.2.6.4). Also, all reportable anticipated and unanticipated protocol events/problems and amendments that are submitted to the IRB are also reviewed by the DSMC Chair or designee and QA manager without any additional reporting requirements from the study staff (2.2.7.3.)

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Appendices

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:

Your birthdate (Day, Month, Year):

Today's date (Day, Month, Year):

_____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4

25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

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

Directions: We are interested in knowing how your experience of having cancer affects your Quality of Life. Please answer all of the following questions based on your life **at this time**.

Please circle the number 0-10 that best describes your experiences:

Physical Well Being

To what extent are the following a problem for you:

1. Fatigue
no problem 0 1 2 3 4 5 6 7 8 9 10 **severe problem**

2. Appetite changes
no problem 0 1 2 3 4 5 6 7 8 9 10 **severe problem**

3. Aches or pain
no problem 0 1 2 3 4 5 6 7 8 9 10 **severe problem**

4. Sleep changes
no problem 0 1 2 3 4 5 6 7 8 9 10 **severe problem**

5. Constipation
no problem 0 1 2 3 4 5 6 7 8 9 10 **severe problem**

6. Nausea
no problem 0 1 2 3 4 5 6 7 8 9 10 **severe problem**

7. **Menstrual changes or fertility**
no problem 0 1 2 3 4 5 6 7 8 9 10 **severe problem**

8. Rate your **overall physical health**
extremely poor 0 1 2 3 4 5 6 7 8 9 10 **excellent**

Psychological Well Being

9. How difficult is it for you to **cope** today as a result of your disease and treatment?
Not at all difficult 0 1 2 3 4 5 6 7 8 9 10 **very difficult**

10. How good is your **quality of life**?
Extremely poor 0 1 2 3 4 5 6 7 8 9 10 **excellent**

11. How much **happiness** do you feel?
None at all 0 1 2 3 4 5 6 7 8 9 10 **a great deal**

12. Do you feel like you are **in control of things in your life?**
Not at all 0 1 2 3 4 5 6 7 8 9 10 **completely**

13. How **satisfying** is your life?
Not at all 0 1 2 3 4 5 6 7 8 9 10 **completely**

14. How is your present ability **to concentrate or to remember** things?
Extremely poor 0 1 2 3 4 5 6 7 8 9 10 **excellent**

15. How **useful** do you feel?
Not at all 0 1 2 3 4 5 6 7 8 9 10 **extremely**

16. Has your illness or treatment caused changes in your **appearance**?
not at all 0 1 2 3 4 5 6 7 8 9 10 **extremely**

17. Has your illness or treatment caused changes in your **self concept** (the way you see yourself)?
Not at all 0 1 2 3 4 5 6 7 8 9 10 **extremely**

How distressing were the following aspects of your illness and treatment?

18. **Initial diagnosis**
not at all 0 1 2 3 4 5 6 7 8 9 10 **very distressing**
distressing

19. **Cancer treatments** (i.e. chemotherapy, radiation, or surgery)
not at all 0 1 2 3 4 5 6 7 8 9 10 **very distressing**
distressing

20. **Time since my treatment** was completed
not at all 0 1 2 3 4 5 6 7 8 9 10 **very distressing**
distressing

21. How much **anxiety** do you have?
not at all 0 1 2 3 4 5 6 7 8 9 10 **a great deal**

22. How much **depression** do you have?
not at all 0 1 2 3 4 5 6 7 8 9 10 **a great deal**

To what extent are you <u>fearful</u> of:

23. Future diagnostic tests
no fear 0 1 2 3 4 5 6 7 8 9 10 **extreme fear**

24. A second cancer

no fear 0 1 2 3 4 5 6 7 8 9 10 **extreme fear**

25. Recurrence of your cancer

no fear 0 1 2 3 4 5 6 7 8 9 10 **extreme fear**

26. Spreading (metastasis) of your cancer

no fear 0 1 2 3 4 5 6 7 8 9 10 **extreme fear**

Social Concerns

27. How **distressing** has your illness been for your family?

Not at all 0 1 2 3 4 5 6 7 8 9 10 **a great deal**

28. Is the amount of **support** you receive from others sufficient to meet your needs?

Not at all 0 1 2 3 4 5 6 7 8 9 10 **a great deal**

29. Is your continuing health care interfering with your **personal relationships**?

Not at all 0 1 2 3 4 5 6 7 8 9 10 **a great deal**

30. Is your **sexuality** impacted by your illness?

Not at all 0 1 2 3 4 5 6 7 8 9 10 **a great deal**

31. To what degree has your illness and treatment interfered with your **employment?**

No problem 0 1 2 3 4 5 6 7 8 9 10 **severe problem**

32. To what degree has your illness and treatment interfered with your **activities at home**?

No problem 0 1 2 3 4 5 6 7 8 9 10 **severe problem**

33. How much **isolation** do you feel is caused by your illness or treatment?

None 0 1 2 3 4 5 6 7 8 9 10 **a great deal**

34. How much **financial burden** have you incurred as result of your illness and treatment?

None 0 1 2 3 4 5 6 7 8 9 10 **a great deal**

Spiritual Well Being

35. How important to you is your participation in **religious activities** such as praying, going to church?

Not at all 0 1 2 3 4 5 6 7 8 9 10 **very important**
important

36. How important to you is other **spiritual activities** such as meditation?

Not at all 0 1 2 3 4 5 6 7 8 9 10 **very important**
important

37. How much has your **spiritual life** changes as a result of cancer diagnosis?

Less important 0 1 2 3 4 5 6 7 8 9 10 **more important**

38. How much **uncertainty** do you feel about your future?

Not at all uncertain 0 1 2 3 4 5 6 7 8 9 10 **very uncertain**

39. To what extent has your illness made **positive changes** in your life?

None at all 0 1 2 3 4 5 6 7 8 9 10 **a great deal**

40. Do you sense a **purpose/mission** for your life or a reason for being alive?

None at all 0 1 2 3 4 5 6 7 8 9 10 **a great deal**

41. How **hopeful** do you feel?

Not at all hopeful 0 1 2 3 4 5 6 7 8 9 10 **very hopeful**

Herth Hope Index

Listed below are a number of statements. Read each statement and place an [X] in the box that describes how much you agree with the statement right now.

	Strongly Disagree	**Disagree**	**Agree**	**Strongly Agree**
1. I have a positive outlook toward life.				
2. I have short and/or long range goals.				
3. I feel all alone.				
4. I can see possibilities in the midst of difficulties.				
5. I have a faith that gives me comfort.				
6. I feel scared about my future.				
7. I can recall happy/joyful times.				
8. I have deep inner strength				
9. I am able to give and receive caring/love.				
10. I have a sense of direction.				
11. I believe that each day has potential.				
12. I feel my life has value and worth.				

Symptom Distress Scale

Below are 5 different numbered statements. Thin about what each statement says, then place a circle around the one statement that most closely indicates how you have been feeling lately. The statements are ranked from 1 to 5, where number one indicates no problem and number five indicates the maximum amount of problems. Numbers two through four indicate you feel somewhere in between the two extremes. Please circle one number on each line.

Degrees of Distress

Nausea (1)

1	2	3	4	5
I seldom if ever have nausea.	I have nausea once in a while.	I have nausea fairly often.	I have nausea half the time at least.	I have nausea continually.

Nausea (2)

1	2	3	4	5
When I do have nausea, it is very mild.	When I do have nausea, it is mildly distressing.	When I have nausea, I feel pretty sick.	When I have nausea, I usually feel very sick.	When I have nausea, I am as sick as I could possibly be.

Appetite

1	2	3	4	5
I have my normal appetite and enjoy good food.	My appetite is usually, but not always, pretty good.	I don't really enjoy my food.	I have to force myself to eat food.	I cannot stand the thought of food.

Insomnia

1	2	3	4	5
I sleep as well as I always have.	I occasionally have trouble getting to sleep and staying asleep.	I frequently have trouble getting to sleep.	I have difficulty getting to sleep and staying asleep almost every night.	It is almost impossible for me to get a decent night's sleep.

Pain (1)

1	2	3	4	5
I almost never have pain.	I have pain once in a while.	I have pain several times a week.	I am usually in some degree of pain.	I am in some degree of pain almost constantly.

Pain (2)

1	2	3	4	5
When I do have pain pain, it is very Mild.	When I do have pain, it is mildly distressing.	When I do have pain, it is usually fairly intense.	The pain I have is very intense	The pain I have is almost unbearable.

Fatigue

1	2	3	4	5
I seldom feel tired or fatigued.	There are periods when I am rather Tired or fatigued.	There are periods when I am quite tired and fatigued.	I am usually very tired and fatigued.	Most of the time, I feel exhausted.

Bowel

1	2	3	4	5
I have my normal bowel pattern.	My bowel pattern Occasionally causes me some discomfort.	My present bowel pattern occasionally causes me considerable discomfort.	I am usually in considerable discomfort because of my present bowel pattern.	I am in almost constant discomfort because of my Bowel pattern.

Concentration

1	2	3	4	5
I have my normal ability to concentrate.	I occasionally have trouble Concentrating.	I occasionally have considerable Trouble Concentraasting.	I usually have considerable difficulty concentrating.	I just can't seem to concentrate at all.

Appearance

1	2	3	4	5
My appearance has basically not changed.	Occasionally I am concerned about The worsening of my physical appearance.	I am not often concerned that my appearance is worsening.	Most of the time I am concerned that my physical appearance is worsening.	The worsening of my physical appearance is a constant, preoccupying concern.

Breathing

1	2	3	4	5
I usually breathe normally.	I occasionally Have trouble breathing.	I often have trouble breathing.	I can hardly ever Breathe as easily as I want.	I almost always have severe Trouble with my breathing.

Outlook

1	2	3	4	5
I am not worried or frightened about the future.	I am slightly worried but not Frightened about Things.	I am worried frightened about things.	I am very worried and frightened About things.	I am terrified by thoughts of the Future.

Cough

1	2	3	4	5
I seldom cough.	I have an occasional cough.	I often cough.	I often cough, and Occasionally have severe coughing spells.	I often have persistent and severe coughing spells.

Trust Scale

How much do you trust your physician(s) …..

	Completely	Mostly	Somewhat	A little	Not at all
1. To put your health and well-being above keeping down the health plan's costs?					
2. To keep personally sensitive medical information private?					
3. To provide you with information on all potential medical options and not just options covered by the health plan?					
4. To refer you to a specialist when needed?					
5. To admit you to the hospital when needed?					
6. To make appropriate medical decisions regardless of health plan rules and guidelines?					
7. Judgment about your medical care?					
8. To perform necessary medical tests and procedures regardless of costs?					
9. To offer you high-quality medical care?					
10. To perform only medically necessary tests and procedures?					

Pancreatic Cancer Survivor Survey

Subject ID _____ **Date** _____
Pancreatic Cancer Survivor Research Participant
Baseline Survey

1. When did you decide whether or not you wanted to join the research study? Check only one answer.
   - ☐ Before arriving at Hopkins
   - ☐ During my visit at Hopkins
   - ☐ After my first visit at Hopkins
   - ☐ Still have not decided

2. When did you decide whether or not you wanted to join the research study? Check only one answer.
   - ☐ As soon as I first heard about it
   - ☐ When I first met the study staff (doctor, nurse, assistant)
   - ☐ After hearing what the research study was all about
   - ☐ After I felt that I really understood the study
   - ☐ Still have not decided

3. Did you know about the research study before you came to Hopkins?
   ☐ Yes ☐ No

   If yes, how did you know about the research study?
   - ☐ TV report or news ☐ Newspaper ☐ Magazine
   - ☐ Internet search ☐ Advocacy group ☐ Patient
   - ☐ Spouse or significant other ☐ Family member ☐ Friend
   - ☐ Primary or local oncologist ☐ Primary or local general health practitioner
   - ☐ Other. Specify type _____

4. What information was most helpful in making the decision about joining the research study? Check only one answer.
   - ☐ Discussion
   - ☐ Informed consent form
   - ☐ Other. Specify: _____

5. Who influenced your decision to join the research study? Check all that apply.

☐ Study doctor ☐ Study nurse ☐ Study assistant
☐ Informed consent form ☐ Media ☐ Other patients
☐ Spouse or significant other ☐ Family member ☐ Friend
☐ Primary or local oncologist ☐ Primary or local general health practitioner
☐ Cancer center staff other than study doctor, nurse, assistant. List staff's role, if known (for example: registrar, secretary, technician, chaplin, etc.)_____
☐ No one

If one person helped you to decide more than the other,
circle that one person from the above list.

6. How many people came with you to Hopkins to learn about the research study?

□ Just me □ One person □ Two people
□ Three people □ Four people □ Five or more people

Subject ID _____ **Date _____**

7. After you learned all about the research study from the study team at Hopkins, did you discuss the research study with anyone before making the decision?

□ Yes □ No

If yes, who? Check all that apply.

□ Spouse or significant other
□ Son…….. Check age □ less than 16 □ 16-21 □ 22-34 □ 35-49 □ 50 or older
□ Daughter..Check age □ less than 16 □ 16-21 □ 22-34 □ 35-49 □ 50 or older
□ Mother □ Father □ Mother-in law □ Father-in-law
□ Sister □ Brother □ Aunt □ Uncle
□ Close friend □ Distant friend □ Patient with same illness
□ Local oncologist □ Local general practitioner □ Local nurse

If one person helped you to decide more than the other,
circle that one person from the above list.

8. About how much time did you think about your decision to join the research study?

□ Less than an hour □ 1-2 hours □ 3-4 hours
□ Almost a full day □ 1-2 days □ 3-4 days
□ Almost a full week □ 1-2 weeks □ 3-4 weeks

9. What would have helped to make the decision easier?

_____

_____

10. Did you receive adequate information to make the decision about being in the research study? □ Yes □ No

11. Are you satisfied with your decision? □ Yes □ No

12. Do you basically understand the research study? □ Yes □ No

13. Are you aware of any possible conflict of interest within the research study? □ Yes □ No

14. What lead you to above response about the possible conflict of interest?
Check all that apply.

Information from:

□ Study doctor □ Study nurse □ Study assistant
□ Informed consent form □ Media □ Other patients
□ Spouse or significant other □ Family member □ Friend
□ Primary or local oncologist □ Primary or local general health practitioner
□ Cancer center staff other than study doctor, nurse, assistant. List staff's role, if known (for example: registrar, secretary, technician, chaplin, etc.)_____

15. Did the informed consent form mention any possible conflict of interest?
□ Yes □ No

Subject ID _____ **Date _____**

16. Do you have other options besides this research study?
□ Yes □ No

<u>If yes,</u> what options are available to you? Check all that apply.
□ Other research studies □ Standard therapy
□ Additional consultation (2nd or 3rd opinion) □ No therapy
□ Complementary therapy □ Hospice care
□ Other _____

17. Do you have any advance directives?

□ Yes

<u>If yes</u>,
Do you have a living will? □ Yes □ No
Do you have a durable power of attorney for health care? □ Yes □ No
Is this information in your medical records at Hopkins? □ Yes □ No

□ No

<u>If no</u>,
Do you know what advance directives are? □ Yes □ No
Have you received information about advance directives? □ Yes □ No
Do you need more information about advance directives? □ Yes □ No

What is the **<u>one</u>** main reason why you do not have advance directives?
□ Need more information □ Not needed now
□ Too much trouble □ Cannot find the forms
□ Too difficult to think about now □ Don't understand the forms
□ Waste of time □ Can't decide what to do
□ Other_____

Protocol No.	Participant Number	Participant Initials	Vaccine : _____
J-0619			Date vaccine administered: ___/___/___

RESEARCH PARTICIPANT DIARY - VACCINE REACTIONS

Vaccine site reactions	Start date	Stop date	Location	Size (Example, size of a dime, etc.)	Action taken, if any (Example, aloe vera, vitamin E gel, etc.)
Redness					
Swelling					
Tenderness				----------	
Itching				----------	

Other Reactions	Start date	Stop date	Describe	Action Taken

Call [redacted] or [redacted] before taking any new medications and if you have any questions.

_____ Research participant's signature & date

_____ Reviewer's signature & date

Continued on the next page

Protocol No.	Participant Number	Participant Initials	Vaccine : _____
J-0619			Date vaccine administered: ___/___/___

HEALTH / MEDICAL COMPLAINTS

If you experience any health/medical complaints, record this information below.

Describe what you experienced	Date started	Date stopped	Actions taken (medications, procedures, etc.)

MEDICATIONS

Record any changes in doses and the stop dates of current medications. Record any new medications (prescription and/or over-the-counter, including herbal medications and vitamins) taken.

Name of medication, dose and frequency	Reason	Date started	Date stopped

_____ Research participant's signature and date

_____ Reviewer's signature and date

☐ check if this is the last page to record your health/medical complaints and medicines for this cycle.