Official Title: A Phase 2, Multicenter Study of FOLFIRINOX Followed by Ipilimumab in Combination with Allogeneic GM-CSF Transfected Pancreatic Tumor Vaccine in the Treatment of Metastatic Pancreatic Cancer

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NCI Supplied Agent: Ipilimumab (NSC 732442)

Investigational Agent: Allogeneic GM-CSF Transfected Pancreatic Tumor Vaccine (Panc 10.05 pcDNA-1/GM-Neo, Panc 6.03 pcDNA-1/GM-Neo)

Commercial Agents: 5- Fluorouracil, irinotecan, leucovorin, and oxaliplatin

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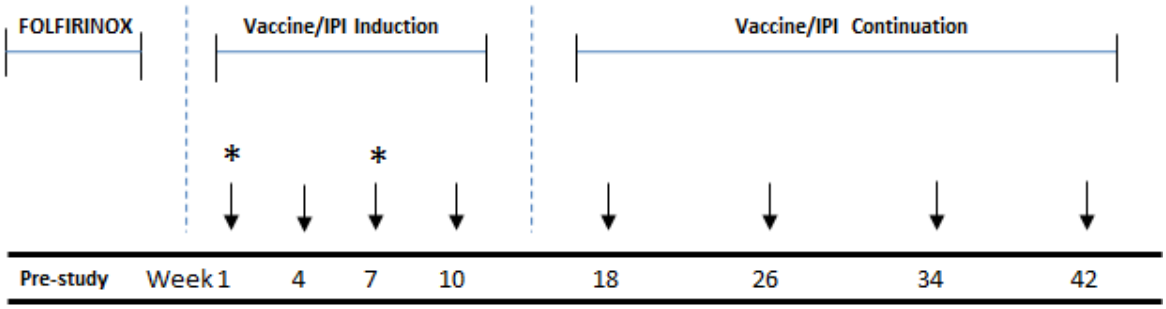

Treatment and assessment schema (Arm A). Patients with stable disease on FOLFIRINOX will be enrolled. The Vaccine/IPI induction phase will consists of 4 treatments separated by 3 weeks. The Vaccine/IPI continuation phase will consists of treatments every 8 weeks. The arrows represent treatment administration and peripheral blood lymphocyte (PBL) and serum collection. * Denotes timing for pre and post treatment 2 tumor biopsies. Arm B will continue chemotherapy with FOLFIRINOX. PBLs and serum will be collected at baseline and after 4 doses. Tumor biopsies are optional in Arm B.

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1. OBJECTIVES

1.1 Primary Objectives

To compare the overall survival (OS) of patients with metastatic pancreatic cancer with stable disease on FOLFIRINOX who then receive ipilimumab and the allogeneic GM-CSF transfected pancreatic tumor vaccine to patients who continue to receive FOLFIRINOX.

1.2 Secondary Objectives

1.2.1 To evaluate safety and characterize toxicities, specifically immune-related adverse events, of ipilimumab in combination with the allogeneic GM-CSF transfected pancreatic tumor vaccine in patients with metastatic pancreatic adenocarcinoma.

1.2.2 To assess progression-free survival (PFS), immune-related progression-free survival (irPFS), and duration of response in patients receiving treatment.

1.2.3 To assess the objective response rate by RECIST and immune-related response criteria in patients receiving treatment.

1.2.4 To measure tumor marker kinetics (CA 19-9) in patients receiving treatment.

1.3 Exploratory Objectives

1.3.1 To collect peripheral blood lymphocytes and serum to identify potential therapeutic targets and biomarkers and predictors of response and autoimmune toxicity. We will correlate induction of antigen specific T cell responses to mesothelin and changes in mesothelin-specific T cell epitope repertoire with OS. We will test if telomere length of lymphocytes can serve to help predict response. Induction of galectin-3 antibody responses will be correlated with response. Proteomic approaches will be used on pre and post treatment sera to identify targets and biomarkers of response or toxicity.

1.3.2 To collect archived tissue and pre and post treatment biopsies to test for predictors of response and future targets for combinatorial therapy. Next generation genome sequencing will be used to identify immune responsive disease subtypes and immunohistochemistry will be used to characterize the nature of tumors and immune infiltrates in responsive subsets. Furthermore, upregulation of immune inhibitory molecules in the pre or post treatment samples may identify additional therapeutic targets.

1.4 Study Design

This study is a randomized phase II study to compare the overall survival of patients with stable metastatic pancreatic adenocarcinoma on FOLFIRINOX who then receive ipilimumab (IPI) and the allogeneic GM-CSF transfected pancreatic tumor vaccine to patients who continue to receive FOLFIRINOX.

Ninety-two patients with metastatic pancreatic cancer who are being treated with FOLFIRINOX will be enrolled. Patients will receive 8-12 doses of FOLFIRINOX as standard of care prior to enrolling on the study. Dose modifications and variations of the FOLFIRINOX regimen are acceptable prior to enrolling on the study, and these modified doses will be counted toward the required 8-12 doses. If the patient has stable disease (SD) or better after the 8th dose, they can be considered for the study. No more than 12 prior doses of FOLFIRINOX will be allowed. Of note, the median number of cycles given in the FOLFIRINOX study was 10 cycles (range 1-47). Patients will be stratified based on the number of cycles of FOLFIRINOX (8 cycles or > 8 cycles) and by center.

Patients will be randomized 1:1 to Arm A (Vaccine + IPI) or Arm B (continue chemotherapy). Patients on Arm B will be encouraged to stay on FOLFIRINOX every 2 weeks if tolerated. However, because of the cumulative toxicity of the regimen, physicians may choose at some point to modify the regimen based on standard of care practice.

Patients who are randomized will be considered in the final analysis. Subjects who drop out of the study due to reasons other than disease progression, death, or toxicity may be replaced at the discretion of the sponsor. Subjects whose death is unequivocally accidental and unrelated to cancer or its treatment may also be replaced.

Treatment and Assessment Plan. Patients on Arm A will receive Vaccine + IPI every 3 weeks x 4 doses then Vaccine + IPI every 8 weeks. Patients that begin treatment on study after approval of protocol version 6.0 will receive IPI at a dose of 3 mg/kg given intravenously (IV). Arm A patients that received treatment prior to approval of protocol version 6.0 will continue to receive IPI at a dose of 10mg/kg. The Vaccine contains 5 x 10^8cells and will be administered intradermally (**see schema**). Arm A treatments will be administered at Weeks 1, 4, 7, and 10. Disease status will be assessed at Weeks 1, 10, and 18. Patients who are clinically stable may stay on study. At the Week 18 evaluation, patients who have had evidence of a response or stabilization of disease will be offered a continuation of therapy where they will receive IPI and Vaccine every 8 weeks until progression or unacceptable toxicity. Patients that are required to stop treatment with IPI due to toxicity may stay on study and receive Vaccine in combination with low lose cyclophosphamide (200 mg/m^2) until progression or unacceptable toxicity. Patients on Arm A will not receive concurrent chemotherapy. Patients on Arm B will continue to receive FOLFIRINOX on day 1 of a 14 day cycle, and their disease status will be evaluated after every four doses. Patients on Arm B will be encouraged to stay on FOLFIRINOX if tolerated. However, because of the cumulative toxicity of the regimen, physicians may choose at some point to modify the regimen based on standard of care practice. Acceptable modified options could include 5-FU alone, capecitabine, FOLFOX, FOLFIRI, or FOLFIRINOX on a 21 day cycle. Patients on Arm B will receive chemotherapy per standard protocols and continue based on response and tolerability. If patients choose to resume care with their primary oncologists, this will be allowed but data on treatments, response, and survival will continue to be collected.

On Arm A, peripheral blood lymphocytes (PBL) and serum will be collected with each treatment for evaluation of immune responses (e.g. mesothelin-specific T cell responses). On Arm B, PBLs and serum will be collected at baseline and after 4 doses. Attempts to obtain archived tumor specimens will be made on all patients. On Arm A, pretreatment and post treatment tumor biopsies

will be collected (if a patient's tumor is thought to be reasonably safe and easy to biopsy) to assess tumor characteristics and immune infiltrates. Additional optional biopsies may be obtained later in the course of therapy in responding patients. Biopsies will be considered optional in Arm B. Furthermore, given that the patients will be responding to chemotherapy on enrollment, it may be difficult to find tumors that can be easily biopsied.

For purposes of determining unacceptable toxicity during the initial 18 week treatment phase, patients on Arm A will be followed for drug related ≥ grade 4 AEs or grade 3 AE including IRAEs not improving to ≤ grade 2 under therapy within 2 weeks. In addition, ≥ grade 2 eye pain or reduction of visual acuity that does not respond to topical therapy and does not improve to ≤ grade 1 severity within 2 weeks of starting therapy, or requires systemic therapy is an unacceptable toxicity. The unacceptable toxicity rate will be continuously monitored and should not be > 33%. Patients that are receiving a continuation of therapy every 8 weeks will also be continuously monitored for unacceptable toxicities. If the rate of unacceptable toxicities in these patients is greater than 33%, then the continuation of treatment will be extended to 12 weeks.

All patients will be followed for survival status by telephone, email, or in clinic once off study. Contact will occur every 12 weeks (or until study termination) to evaluate OS, PD, subsequent cancer therapies, and AEs. Adverse events 70 days after the last dose of investigational agent (Arm A) will only be recorded if deemed possibly, probably, or definitely related to the investigational agent. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

2. BACKGROUND

2.1 Study Disease

Pancreatic adenocarcinoma remains an aggressive disease with a median survival of about 6 months when treated with single agent gemcitabine for metastatic disease. Even with the most aggressive chemotherapy regimen, FOLFIRINOX (5-flourouracil, irinotecan, oxaliplatin), median survival is 11 months (Conroy *et al*, 2011). Novel approaches, such as immunotherapy, are showing promise in this very difficult cancer.

2.2 Ipilimumab

Ipilimumab (MDX-010, MDX-CTLA4, BMS-734016) is being developed by CTEP as an anticancer agent in collaboration with Bristol-Myers-Squibb (BMS). On March 25, 2011, the FDA approved ipilimumab injection (YERVOY, BMS) for the treatment of unresectable or metastatic melanoma. Ipilimumab is a human $IgG_1\kappa$ monoclonal antibody (mAb); it is specific for human cytotoxic T lymphocyte-associated antigen-4 (CTLA-4, CD152) expressed on activated T cells. Ipilimumab is now produced and formulated from transfected Chinese hamster ovary (CHO) cells.

CTLA-4 is a negative regulator of T-cell responses following T-cell stimulation (Thompson and Allison, 1997; Kuhns *et al*., 2000). CTLA-4 knockout mice suffer from a fatal lymphoproliferative disorder, supporting the idea that CTLA-4 functions as a negative regulator of T-cell responses *in*

vivo (Tivol *et al*., 1995; Waterhouse *et al*., 1995; Chambers *et al*., 1997). Disrupting CTLA-4 interaction with its ligands B7-1 (CD80) and B7-2 (CD86), which are expressed on antigen-presenting cells (APCs), with ipilimumab, augments immune responses (Investigator Brochure, 2011). *In vivo* blockade of CTLA-4, utilizing anti-CTLA-4 mAb, induced regression of established tumors and enhanced antitumor immune responses in several murine tumor models. Blockade of CTLA-4-mediated signals is effective in inducing rejection of immunogenic cancers in mice. Moreover, when anti-CTLA-4 mAb is used in conjunction with granulocyte macrophage-colony stimulating factor (GM-CSF)-secreting tumor vaccines, poorly immunogenic cancers in mice are rejected. These findings suggest that CTLA-4 blockade, alone or in combination with antigenic stimulation and other immune modulating agents can induce a potent antitumor response.

Pharmacology of Ipilimumab

In vitro studies were performed with ipilimumab to demonstrate that it is specific for CTLA-4, actively inhibits CTLA-4 interactions with B7.1 and B7.2, does not show any cross-reactivity with human B7.1 or B7.2 negative cell lines, and stains the appropriate cells without non-specific cross-reactivity in normal human tissues. Ipilimumab does cross-react with CTLA-4 in non-human primates including cynomolgus monkeys. Blockade of CTLA-4/B7 interactions enhanced T-cell responses to CD3 / CD28, peptide antigens, or superantigens in mice (Walunas, *et al.,* 1994; Kearney, *et al.,* 1995; Krummel and Allison 1995; Krummel, Sullivan, and Allison, 1996). CTLA-4 knockout mice appear to have spontaneously activated T cells evident at approximately 1 week after birth, followed by rampant lymphoproliferation and lymphadenopathy. These mice die at approximately 3 weeks of age, either as a result of polyclonal T-cell expansion and tissue destruction or as a result of toxic shock resulting from lymphokine production. Genetically engineered mice heterozygous for CTLA-4 (CTLA-4+/-), appeared healthy and gave birth to healthy CTLA-4+/- heterozygous offspring. Mated CTLA-4+/- heterozygous mice also produced offspring deficient in CTLA-4 (homozygous negative, CTLA-4-/-). Since thymocyte differentiation and selection proceed normally in CTLA-4-deficient mice, the rampant T-cell expansion that occurs in the mice indicates that CTLA-4 plays a critical role in down-regulating post- thymic T-cell responses in the periphery following stimulation of naïve, memory, and effector T cells (Krummel, Sullivan, and Allison, 1996).

Pharmacokinetics

The pharmacokinetics (PK) of ipilimumab was studied in 499 patients with unresectable or metastatic melanoma who received doses of 0.3, 3, or 10 mg/kg administered once every 3 weeks (q3w) for four doses. Peak concentration (Cmax), trough concentration (Cmin), and area under the curve (AUC) of ipilimumab were found to be dose proportional within the dose range examined. Upon repeated dosing of ipilimumab administered q3w, ipilimumab clearance was found to be time-invariant, and minimal systemic accumulation was observed as evident by an accumulation index of 1.5-fold or less. Ipilimumab steady-state concentration was reached by the third dose. The following mean (percent coefficient of variation) parameters were generated through population PK analysis: terminal half-life of 14.7 days (30.1%); systemic clearance (CL) of 15.3 mL/h (38.5%); and volume of distribution at steady-state (Vss) of 7.21 L (10.5%). The mean (±SD) ipilimumab Cmin achieved at steady-state with the 3-mg/kg regimen was 21.8 mcg/mL (±11.2).

Specific Populations: Cross-study analyses were performed on data from patients with a variety of conditions, including 420 patients with melanoma who received single or multiple infusions of ipilimumab at doses of 0.3, 3, or 10 mg/kg. The effects of various covariates on ipilimumab PK were assessed in population PK analyses.

Ipilimumab CL increased with increasing body weight; however, no dose adjustment of ipilimumab is required for body weight after administration on a mg/kg basis.

The following factors had no clinically meaningful effect on the CL of ipilimumab: age (range 26 to 86 years), gender, concomitant use of budesonide, performance status, HLA-A2*0201 status, positive anti-ipilimumab antibody status, prior use of systemic anticancer therapy, or baseline lactate dehydrogenase (LDH) levels. The effect of race was not examined as there were insufficient numbers of patients in non-Caucasian ethnic groups.

Renal Impairment: Creatinine clearance at baseline did not have a clinically important effect on ipilimumab PK in patients with calculated creatinine clearance values of 29 mL/min or greater.
Hepatic Impairment: Baseline AST, total bilirubin, and ALT levels did not have a clinically important effect on ipilimumab PK in patients with various degrees of hepatic impairment.

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Nonclinical Toxicology

Please note relevant toxicity for single agent ipilimumab has been almost completely derived from clinical studies.

In a study using cynomolgus macaques, anti-melanocyte responses were observed in animals given up to four doses of 10 mg/kg ipilimumab after receiving a melanoma cell vaccine (Keler *et al*., 2003). Depigmentation has been observed in other nonclinical immunotherapy studies that involve treatment with melanoma peptides (Hara *et al*., 1995; Naftzger *et al*., 1996; Bloom *et al*., 1997; Overwijk *et al*., 1998; Weber *et al*., 1998; Overwijk *et al*., 1999). The symptoms in animals appear to resemble vitiligo observed in clinical immunotherapy trials of melanoma patients and may be an unavoidable consequence of treatment (Rosenberg and White, 1996).

Additional repeat-dose toxicity studies conducted using cynomolgus macaques demonstrated that the IV administration of ≤30 mg/kg every 3 days for three doses, 10 mg/kg weekly for 1 month, 1 mg/kg weekly for 10 weeks, or 10 mg/kg monthly for 6 months was generally well tolerated, without significant clinical, immunotoxicological, or histopathological findings (Investigator Brochure, 2011). However, when ipilimumab was administered in combination with another immunomodulatory antibody (BMS-663513, a fully human anti-CD137 mAb) and simian immunodeficiency virus (SIV) DNA, two immune-related adverse events (irAEs) were observed: severe colitis requiring euthanasia in one monkey and reversible dermatitis/rash in the inguinal area and peripheral lymphadenopathy in another monkey.

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Other Clinical Studies with Ipilimumab

Renal cell carcinoma (RCC)

Yang and colleagues presented data on a phase 2 study of ipilimumab conducted in patients with metastatic RCC (Yang *et al*., 2007). Sequential cohorts received either 3 mg/kg followed by 1 mg/kg or all doses at 3 mg/kg q3w. One of 21 patients receiving the lower dose had a PR. Five of 40 patients at the higher dose had PRs (95% CI, cohort response rate 4 to 27%) and responses were seen in patients who had previously not responded to IL-2. Thirty-three percent of patients experienced grade 3 or 4 irAEs. There was a highly significant association between autoimmune events and tumor regression (response rate = 30% with AE, 0% without AE). The authors concluded that CTLA-4 blockade with ipilimumab induced cancer regression in some patients with metastatic clear cell renal cancer, even if they had not responded to other immunotherapies.

Melanoma (ipilimumab plus bevacizumab)

At the 2011 ASCO meeting Hodi and colleagues presented results on 21 evaluable patients (22 patients enrolled) with unresectable stage III or stage IV melanoma treated with the combination of 10 mg/kg ipilimumab and 7.5 mg/kg bevacizumab on a phase 1 study (Hodi *et al*., 2011). AEs included giant cell arteritis (1), hypophysitis (3), thyroiditis (4), grade 3-4 hepatitis (2), bilateral uveitis (2), and grade 2 colitis (2); 5 patients required systemic steroids and stopped treatment. All toxicities were resolved. Eight PRs and 6 SDs were observed. All responses were durable (>6 months). Post-treatment biopsies in 12 patients revealed activated vessel endothelium with extensive T-cell trafficking non-productive central angiogenesis, and peripheral blood monitoring revealed a marked increase in CD4/CCR7/CD45RO central memory cells in the majority of patients, not seen with ipilimumab alone. The authors concluded that the combination of ipilimumab with bevacizumab can be safely administered with clinical activity and correlatives suggesting synergistic effects.

Bladder cancer

Carthon and colleagues reported immunomodulatory effects following a brief exposure of anti-CTLA-4 in patients with urothelial carcinoma of the bladder requiring surgery (BMS study CA184027) (Carthon *et al*., 2010). 12 patients were enrolled (6 patients received 3 mg/kg/dose of ipilimumab and another 6 patients received 10 mg/kg/dose for two doses prior to surgery). The treatment was found to be tolerable in the cohort of patients with 11 of 12 patients receiving both doses of antibody. Grade 1-2 diarrhea and rash were the most common drug-related AEs. The only noted grade 3 irAEs were ischemic papillopathy and diarrhea, which were both responsive to treatment with steroids.

Liakou and colleagues found that CD4 T cells from peripheral blood and tumor tissues of all bladder cancer patients treated with anti-CTLA-4 antibody had markedly increased expression of inducible costimulator (ICOS) (Liakou *et al*., 2008). These $CD4^{+}ICOS^{hi}$ T cells produced interferon-gamma (IFN-γ) and could recognize the tumor antigen NY-ESO-1. Increase in $CD4^{+}ICOS^{hi}$ cells led to an increase in the ratio of effector to regulatory T cells. The authors indicated that these immunologic changes were reported in both tumor tissues and peripheral blood as a result of treatment with anti-CTLA-4 antibody, and they may be used to guide dosing and scheduling of this agent to improve clinical responses. A sustained increased frequency of $CD4^{+}ICOS^{hi}$ T cells may serve as a biomarker of anti-CTLA-4 activity and/or of clinical benefit for patients who are being treated with this novel agent (Carthon *et al*., 2010).

Pancreatic cancer
Royal and colleagues presented the results on 27 patients (metastatic disease: 20 and locally advanced: 7) (Royal *et al*., 2010). Three subjects experienced ≥ grade 3 irAEs (colitis:1, encephalitis:1, hypophysitis:1). One subject experienced a delayed response after initial progressive disease. In this subject, new metastases after 2 doses of ipilimumab established progressive disease. However, continued administration of the agent per protocol resulted in significant delayed regression of the primary lesion and 20 hepatic metastases with normalization of tumor markers and clinically significant improvement of performance status. The investigators concluded that single agent ipilimumab at 3.0 mg/kg/dose was ineffective for the treatment of advanced pancreatic cancer. However, a significant delayed response in one subject of this trial suggests that immunotherapeutic approaches to pancreatic cancer deserve further exploration.

CTEP-Sponsored Studies

The DCTD, NCI, has sponsored nine studies with ipilimumab including one pilot study (NCI #5744, lymphoma), three phase 1 studies (5708 [ovarian], 6082 [solid tumors], and 7458 [solid tumors]), one phase 1/2 study (6359 [non-Hodgkin's lymphoma]) with single agent ipilimumab, two phase 1 combination studies in prostate cancer with GM-CSF (6032) and with prostate-specific antigen (PSA)-TRICOM vaccine (7207), one phase 2 combination study of ipilimumab with GM-CSF (E1608, melanoma) and one phase 3 study (E1609) of adjuvant ipilimumab therapy versus high-dose interferon alpha-2b in patients with resected high-risk melanoma.

Results from 11 patients (colon, n=3; non-Hodgkin's lymphoma, n=4; prostate, n=4) who received ipilimumab on study 5744 included tumor regression in 2 patients with lymphoma; 1 of whom (follicular lymphoma patient) had a partial response (PR) of 14-month duration (O'Mahony *et al*., 2007). Ipilimumab was well tolerated with predominantly grade 1/2 toxicities. One drug-related grade 3 AE was observed. Tregs, as detected by expression of $CD4^+CD25^+CD62L^+$, declined at early time points but rebounded to levels at or above baseline values at the time of the next infusion. The investigators concluded that ipilimumab treatment depressed Treg numbers at early time points in the treatment cycle but was not accompanied by an increase in vaccine-specific CD8+ T-cell responses in these patients previously treated with a variety of investigational anticancer vaccines.

Hodi and colleagues reported preliminary results on 20 patients (11 metastatic melanoma patients and 9 metastatic ovarian carcinoma patients) on study 5708 (Hodi *et al*., 2008). None of the 11 patients from the metastatic melanoma cohort manifested grade 3 or 4 inflammatory toxicities; however, all subjects revealed mild inflammatory pathologies associated with low-level constitutional symptoms. The most common toxicity (10/11 subjects) was a grade 1-2 reticular and erythematous rash on the trunk and/or extremities that arose between 3 days and 3 weeks after antibody administration and then gradually resolved without specific intervention. Biopsies of involved skin revealed low-grade interface dermatitis, minor to moderate mononuclear infiltrates surrounding the superficial dermal vasculature, and increased mucin deposition in the papillary and reticular dermis. These pathologic features resembled those observed in mild cutaneous forms of systemic lupus erythematosis. Three PRs (range, 21-34+ months) and five events of stable disease (SD) (range, 4-25 months) were observed. One PR and three SDs (2, 4, and 6+ months) were observed in the ovarian carcinoma group. The investigators concluded that selective

targeting of antitumor regulatory T cells (Treg) may constitute a complementary strategy for combination of ipilimumab and GM-CSF-based antigen tumor cell vaccine therapy.

Results from 29 patients with malignancies that were recurrent or progressive after allogeneic hematopoietic cell transplantation (allo-HCT) demonstrated that drug was well tolerated at single doses up to 3 mg/kg (Bashey *et al*., 2009). Four patients experienced organ-specific irAEs of reversible grade 3 arthritis, grade 2 hyperthyroidism, dyspnea, and grade 4 pneumonitis. Three patients had objective responses: one PR lasting for 2 months, and two durable complete responses (CRs). Two additional patients with Hodgkin's disease who had evidence of rapid disease progression prior to ipilimumab treatment achieved SD for 3 and 6 months, following infusion at the 3 mg/kg dose level. Median OS was 24.7 months. At a 3.0 mg/kg dose, active serum concentrations of ipilimumab were maintained for >30 days following a single infusion. Zhou and colleagues reported immunophenotypes of peripheral blood T cells, including T-cell reconstitution, activation, and Treg expression, in 29 patients before and after a single-dose infusion of ipilimumab (Zhou *et al*., 2011). CTLA-4 blockade by a single infusion of ipilimumab increased $CD4^+$ and $CD4^+HLA\text{-}DR^+$ T lymphocyte counts and intracellular CTLA-4 expression at the highest dose level (3.0 mg/kg). There was no significant change in Treg cell numbers after ipilimumab infusion. These data demonstrate that significant changes in T-cell populations occur on exposure to a single dose of ipilimumab.

Harzstark and colleagues reported results on 36 patients with hormone refractory metastatic prostate cancer (Harzstark *et al.*, 2010). Of six patients treated with ipilimumab at a dose of 3 mg/kg, three patients had confirmed PSA declines of ≥50%, with a time to progression (TTP) of 22, 26, and 103 weeks. One of these patients had a PR in hepatic metastases. Grade 3 IrAEs consisted of rash in five patients, panhypopituitarism in one patient, temporal arteritis in one patient, and diarrhea in three patients. Non-irAEs included grade 3 and 4 cerebrovascular events (one patient each), grade 3 angina (one patient), grade 3 atrial fibrillation (one patient), grade 3 fatigue (four patients), and grade 5 pulmonary embolism (one patient). One patient treated at 10 mg/kg had a PSA decline of ≥50% with a TTP of 39 weeks. Higher doses of treatment with MDX-010 + GM-CSF induced the expansion of activated circulating $CD25^+$, $CD69^+$, and $CD8^+$ T cells more frequently than was seen in patients who received the same doses of either MDX-010 or GM-CSF alone (Fong *et al*., 2009). The sera screening with protein arrays showed that the treatment can induce antibody responses to the testicular antigen NY-ESO-1.

Patients with metastatic prostate cancer were treated with ProstVac vaccine and ipilimumab before chemotherapy. The median OS for all patients on study was 31.8 months with a 74% survival probability at 24 months (Madan *et al*., 2010). The median Halabi predicted OS for all patients was 18.5 months. There was no significant difference in OS at different dose levels of antibody (range 1-10 mg). A unique effect of the vaccines on the rate of tumor growth may be a novel method to evaluate the anti-tumor effects of the vaccine (Stein *et al.,* 2011). The authors suggested that the addition of immune checkpoint inhibition may augment the clinical benefit of vaccines.

Ansell and colleagues reported data on 18 treated patients with NHL (Ansell *et al*., 2009). Two clinical responses were observed: one patient with diffuse large B-cell lymphoma (BCL) had an ongoing CR (>31 months), and one with follicular lymphoma had a PR lasting 19 months. In 5 of 16 cases tested, T-cell proliferation to recall antigens was >2 fold increased after ipilimumab

therapy. The investigators have found that blockade of CTLA-4 signaling with the use of ipilimumab is well tolerated at the doses used. Ipilimumab has antitumor activity in patients with BCL, resulting in durable responses in a minority of patients. Ipilimumab at 3 mg/kg monthly for 4 months can be given safely and is the dose that recommended for future combination studies.

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Study Results and Clinical Efficacy

The clinical efficacy of ipilimumab as a single agent at a dose of 3 mg/kg administered q3w for 4 doses has been established in MDX010-20 (a randomized, controlled study in second line, locally advanced/metastatic melanoma), which led to approval of ipilimumab by the FDA. In study CA184024, the addition of 10 mg/kg ipilimumab to dacarbazine led to a prolongation of

overall survival in patients with previously untreated melanoma.

In melanoma studies, disease stabilization in subjects receiving ipilimumab is characteristic of anti-tumor activity. Stable disease, sometimes of long duration, or slow steady decline of tumor lesion size over long periods of time, has been observed. Some subjects demonstrate initial tumor volume increase before response, possibly due to T-cell infiltration as shown by biopsies or to the time required for immunologic activation. Consequently, an initial determination of progressive disease and consequently PFS may not capture all patterns response and may underestimate the clinical activity of ipilimumab. Please see section "Considerations for Using Immune-Related Tumor Assessment Criteria (irRC)."

MDX010-20 (Phase 3, 3 mg/kg, previously treated melanoma)

MDX010-20, a randomized (3:1:1), double-blind, double-dummy study included 676 randomized subjects with unresectable or metastatic melanoma previously treated with one or more of the following: aldesleukin, dacarbazine, temozolomide, fotemustine, or carboplatin. Of these 676 subjects, 403 were randomized to receive ipilimumab at 3 mg/kg in combination with an investigational peptide vaccine with incomplete Freund's adjuvant (gp100), 137 were randomized to receive ipilimumab at 3 mg/kg, and 136 were randomized to receive gp100 alone. The study enrolled only subjects with HLA A2*0201 genotype; this HLA genotype facilitates the immune presentation of the investigational peptide vaccine. The study excluded subjects with active autoimmune disease or those receiving systemic immunosuppression for organ transplantation.

The OS results are shown in the table below.

MDX010-20 Overall Survival Results

	Ipilimumab n = 137	**Ipilimumab + gp100 n = 403**	**gp100 n = 136**
Hazard Ratio (vs gp100) (95% CI)	0.66 (0.51, 0.87)	0.68 (0.55, 0.85)	
p-value	p = 0.0026[a]	p = 0.0004	
Hazard Ratio (vs ipilimumab) (95% CI)		1.04 (0.83, 1.30)	
Median (months) (95% CI)	10 (8.0, 13.8)	10 (8.5, 11.5)	6 (5.5, 8.7)

[a] Not adjusted for multiple comparisons.

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[redacted]

Dose, Schedule, and Regimen

While optimal doses and schedules for ipilimumab have not yet been determined, in proposed proof of principle studies demonstration of efficacy at 10 mg/kg would allow future studies to explore biologic and clinical efficacy at lower doses with reduced toxicity. For most studies in new combinations or settings, a short phase 1 component at 3 mg would be appropriate with a 5 or 6 mg/kg dose added as an additional cohort if needed.

A recommended dose of 10 mg/kg is proposed by the manufacturer for most studies of ipilimumab. In melanoma, a similar survival benefit was demonstrated in phase 3 trials at the 3 mg/kg and at 10 mg/kg with DTIC. However, the incidence of grade $\geq$3 toxicity was 15 and 25% respectively.

Based on Phase 2 studies, response rates of ipilimumab appear to be dose dependent up to 10 mg/kg.

Exposure-response analyses [C_{min}ss Analysis of PK data from patients treated with ipilimumab at 0.3 mg/kg (N=47), 3 mg/kg (N=60) and 10 mg/kg (N=311)], showed that the target C_{min}ss target threshold of 20 mcg/ml was exceeded in 0%, 30% and 95% subjects respectively. The slope of change in absolute lymphocyte count (ALC) correlated with clinical benefit and T-cell activation markers such as HLA-class II expression may also be dose dependent. Responses have not been compared systematically in randomized phase 2 or phase 3 studies in patients with tumor types other than melanoma.

Regarding schedule, the typical schedule for advanced melanoma at present is once q3w for four doses followed by a maintenance phase of four doses every 12 weeks. Of interest, ipilimumab was evaluated in NSCLC and SCLC using a dose of 10 mg/kg given concomitantly or following

initial paclitaxel/carboplatin. When used in the phased schedule, 10 mg/kg significantly improved irPFS and mWHO defined responses but not PFS determined by Response Evaluation Criteria in Solid Tumors (RECIST). There also was a trend for an improvement in OS in both indications. Doses less than 10 mg/kg have not been evaluated in either NSCLC or SCLC.

Studies comparing doses in non-melanoma and combinations have not been widely done. There are also no clear data that peak levels, Cmin, AUC, exposure and number of doses given, or the occurrence of autoimmune events, predict responses in individual patients. We note that the incidence of specific events such as hypophysitis may vary from study to study and with different combinations of agents. The severity and possibly time to onset but not necessarily the frequency of events increases with dose. In addition, there are rare but serious events such as toxic epidermal necrolysis (TEN) for which a dose relationship has not been established. Case report forms should include data on the prior treatment, timing, number of doses, duration of event, response to treatment, and complications to allow comparisons among studies.

Considerations in Using Immune-Related Tumor Assessment Criteria (irRC)

New end point definitions for trials of immunologic agents have been proposed based on novel patterns of clinical activity in malignant melanoma (Wolchok, *et al.*2009; Hoos, *et al.* 2010). These alternative definitions allow time for immunologically mediated effectors to develop that may result in late tumor responses even after initial progression by RECIST. Also, in some patients, tumors necrosis and inflammation may increase tumor size radiographically prior to response. Changing the definitions of OR and PD may alter (increase) the number patients achieving responses and the duration of PFS.

On a protocol by protocol basis, we would consider allowing study treatment to continue during initial progression up to the 12-16 week assessment to allow time for responses to be observed, if the patient is clinically stable, there is no deterioration in PS, and there is no need for immediate additional treatment. While maintaining standard definitions of progression and response, we would allow new lesions and some progression beyond 20% increases in tumor measurements during the initial treatment period to allow time for responses to develop (these delayed tumor responses may be seen in 10-20% of melanoma patients who initially progress during the initial treatment cycles and evaluation).We do not have experience with response patterns with combination therapy nor in diseases other than melanoma.

Note that the proposed irRC have been incorporated as secondary end points in addition to standard criteria and evaluate alternative patterns of response in various disease setting and treatment regimens. A copy of the proposed criteria is presented in **Appendix A**.

Patients who demonstrate mixed responses, stable disease, or objective responses by standard RECIST following initial progression may be identified separately as “delayed SD, PR, or CR”.

Overall Risk/Benefit Assessment

The unique immune-based mechanism of action is reflected in the clinical patterns of anti-cancer activity in some patients. Ipilimumab affects tumor cells indirectly, and measurable clinical effects

emerge after the immunological effects. Tumor infiltration with lymphocytes and the associated inflammation (documented by biopsy in some subjects) is likely the cornerstone of the effect of ipilimumab and can manifest in various patterns of clinical activity leading to tumor control. In some cases, response may be preceded by an apparent increase in initial tumor volume and/or the appearance of new lesions, which may be mistaken for tumor progression on radiological evaluations. Therefore, in subjects who are not experiencing rapid clinical deterioration, confirmation of progression is recommended, at the investigator's discretion, to better understand the prognosis as well as to avoid unnecessarily initiating potentially toxic alternative therapies in subjects who might be benefitting from treatment. Immune-related (ir) response criteria were developed based on these observations to systematically categorize novel patterns of clinical activity and are currently being prospectively evaluated in clinical studies.

In metastatic diseases, stabilization is more common than response, and in some instances is associated with slow, steady decline in tumor burden over many months, sometimes improving to partial and/or complete responses. Thus, the immune-based mechanism of action of ipilimumab results in durable disease control, sometimes with novel patterns of response, which contribute to its improvement in OS.

The immune-based mechanism of action is also reflected in the safety profile. The most common drug-related AEs are immune-mediated, consistent with the mechanism of action of the drug and generally medically manageable with topical and/or systemic immunosuppressants. As previously discussed, the immune-mediated adverse reactions primarily involve the GI tract, skin, liver, endocrine glands, and nervous system.

The early diagnosis of immune-mediated adverse reactions is important to initiate therapy and minimize complications. Immune-mediated adverse reactions are generally manageable using symptomatic or immunosuppressive therapy as recommended through detailed diagnosis and management guidelines, as described fully in the current IB. The management guidelines for general immune-mediated adverse reactions and ipilimumab-related GI toxicities, hepatotoxicity, endocrinopathy, and neuropathy are provided in the appendices of the current IB.

2.3 Allogeneic GM-CSF Transfected Pancreatic Tumor Vaccine

2.3.1 Immunotherapy for Pancreatic Adenocarcinoma

Immunotherapy is a novel approach to the eradication of pancreatic cancer, a relatively chemo-resistant disease. An ideal therapy would recruit and activate tumor specific T cells with a wide range of tumor antigen specificities and generate memory immune responses while limiting toxicity to normal tissues. Several proteins have been identified that are overexpressed in pancreatic cancer such as carcinoembryonic antigen (CEA), mutated k-ras, mucin-1 (MUC1) and gastrin (Hruban, *et al*, 1993; Apostolopoulos, *et al*, 1994; Hammarstrom, *et al*, 1999; Harris, *et al*, 2004). However, these antigens are relatively non-immunogenic. Strategies have included immunization with co-administered immune modulating agents such as GM-CSF or alternative delivery mechanisms such as antigen-pulsed dendritic cells (Marshall, *et al*, 2005). Significant clinical responses have not been demonstrated. This may be due to immune tolerance mechanisms,

inadequate antigens or pooling of antigens, or the inability for the relevant immune cells to localize to appropriate sites for priming or to the sites of disease.

The use of whole-cell vaccines is promising because it delivers a range of peptide antigens without the need for specific knowledge of the relevant target antigens. Preclinical studies show that among tumor cells genetically modified to express various cytokines, GM-CSF is the cytokine most effective in inducing anti-tumor immunity (Dranoff, *et al*, 1993). GM-CSF is an important growth and differentiation factor for dendritic cells, which are potent antigen-presenting cells.

The use of allogeneic tumor cells for vaccine development over autologous tumor cells is attractive for several reasons. Autologous tumor cells are not always available and the production of an autologous vaccine is technically difficult, costly, and inefficient. Supporting the use of allogeneic tumor cells is the characterization of tumor-associated antigens in melanoma, which revealed that regardless of human leukocyte antigen (HLA) type, 50% of tumors share common antigens (Cox, *et al*, 1994; Kawakami, *et al*, 1994). In addition, both preclinical and human data support that the antigen-presenting cells important in GM-CSF based vaccination are host-derived suggesting that the vaccine cells and the host do not have to be HLA compatible (Huang, *et al*, 1994; Huang, *et al*, 1996).

Three clinical trials have been completed, with seven clinical trials ongoing or under analysis, testing the allogeneic GM-CSF secreting tumor vaccine approach alone and in combination with other targeted interventions in patients with resected and metastatic pancreatic cancer. Altogether, 400+ patients have been treated, the majority at doses of $5x10^8$ vaccine cells per vaccination, with up to 6 total cycles or 10 boost vaccinations per patient, without evidence of dose limiting toxicities. These studies have demonstrated the feasibility of vaccine delivery to patients with pancreatic cancer, and its safety given alone and in combination with a number of chemotherapeutic agents and radiation therapy. Immunized lymphocytes from treated patients are being used as an approach for identifying "immune relevant" pancreatic cancer antigens. Below is a summary of the 3 completed trials.

2.3.2 Results of a Phase I Adjuvant Study at Johns Hopkins

This study was the first clinical trial to test the hypothesis that the allogeneic GM-CSF transfected pancreatic tumor vaccine can prime a systemic immune response in subjects with resected pancreatic adenocarcinoma (Jaffee, *et al*, 2001). Fourteen subjects with stage II or III disease received an initial vaccination 8 weeks following resection. This was a dose escalation study in which 3 subjects each received 1×10^7, 5×10^7, and 1×10^8 vaccine cells. An additional 5 subjects received 5×10^8 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. 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 1X 10^8 and in 2 of 5 subjects receiving 5X10^8 vaccine cells.

2.3.3 Follow-up phase II study integrating the whole cell vaccine with chemoradiation for resected pancreatic adenocarcinoma

Johns Hopkins has also completed a follow-up phase II study of 60 patients with resected pancreatic adenocarcinoma based on the results of their phase I experience (Lutz, *et al*, 2011). The highest dose of vaccine from the phase I study (5 X 10^8 vaccine cells) was used and the adjuvant chemotherapy regimen given in sequence with the vaccine was modified to eliminate mitomycin-C as this drug was thought to depress immune function as measured by a decrease in vaccine induced mesothelin specific T cells following chemoradiation. The common toxicities associated with the vaccine in this study included: local vaccine site skin reactions and systemic rashes similar in severity (grade 1-2) to what was observed in the phase I trial. A full description of toxicities is provided in the Investigator's Brochure. The results from this study include the following:

- The administration of the whole cell vaccine is safe and well-tolerated. Treatment related side effects included transient vaccine injection site reactions.
- Systemic GM-CSF levels were evaluated as an indirect measure of the longevity of vaccine cells at the immunizing site. As was observed in the phase I study, GM-CSF levels peaked at 48 hours following the first and second vaccination but peaked earlier following the 3rd and 4th vaccination with diminution in amplitude. Serum GM-CSF levels following vaccine 5 peaked again at 48 hours and returned to vaccine 1 serum levels. The results would suggest the possibility that the potency of an allogeneic vaccine is diminished with repeated monthly vaccinations, but returns to pre-treatment levels with an extended time interval between boosts.
- As recently reported, (88% node (+), 30% margin (+)) the median survival was 24.8 months.
- Post-Immunotherapy induction of mesothelin-specific $CD8^+$ T cells with higher avidity and increased mesothelin epitope recognition (T cell repertoire expansion) correlates with disease free survival (DFS).

The data also support additional boost immunotherapies beyond one year post surgery in future studies.

2.3.4 Phase II Trial of The GM-CSF Secreting, Allogeneic Vaccine Alone And in Sequence with Immune Modulating Doses of Cy in Patients with Stage 4 Pancreatic Cancer

Immune tolerance remains a major barrier to effective vaccine therapies. In particular, regulatory T cells ($CD4^+CD25^+$) have been shown to play a role in inducing $CD8^+$ T cell tolerance.

Manipulating the regulatory T cells may result in more effective vaccine strategies. In mouse models, immune modulating doses of Cyclophosphamide (Cy) in combination with GM-CSF based cell vaccines have been shown to improve tumor rejection from 0% to 10 - 30% in the HER-2/neu transgenic mouse model. The addition of Cy allowed the activation of high-avidity $RNEU_{420-429}$-specific $CD8^+$ T cells in the mice, which rejected tumor. This effect was abrogated by $CD4^+CD25^+$ T cells derived from neu-N transgenic mice suggesting that Cy before vaccination may block T regulatory cells allowing for recruitment of latent high-avidity neu-specific $CD8^+$ T cells (Ercolini, *et al*, 2005).

A feasibility study of the GM-CSF-secreting, allogeneic vaccine administered alone or in sequence with Cy in patients with stage 4 pancreatic cancer, has been completed. This study was an open label study sponsored by Cell Genesys, Inc. consisting of two cohorts: Cohort A- 30 patients administered a maximum of six doses of vaccine using our two pancreatic cancer cell lines (2.5X 10^8 of each cell line) intradermally at 21 day intervals; Cohort B- 20 patients administered Cy 250 mg/m^2 IV one day prior to each vaccination (administered as in Cohort A). The primary objective was to evaluate safety and efficacy of the vaccine administered alone or in sequence with Cy. Secondary objectives included: time to disease progression (TTP), median overall survival (OS), and assessment of the feasibility of detecting mesothelin-specific T cell responses in pancreatic cancer patients with advanced disease (Laheru, *et al*, 2008).

First, the administration of a GM-CSF-secreting, allogeneic pancreatic tumor vaccine either alone or in sequence with Cy is feasible, safe, and tolerated by patients with advanced pancreatic cancer, the majority of which had received ≥ 2 prior chemotherapy regimens. Second, serum GM-CSF levels peaked at 48 hours post vaccination consistent with published results describing the administration of this and other GM-CSF-secreting vaccines when given in the adjuvant setting. Serum GM-CSF levels were detected at 48 hours after repeated vaccinations, suggesting that the vaccine cells are not rapidly cleared by an allogeneic response with repeat administration. Third, stable disease lasting a median of 18 weeks was observed in 16.7% of patients treated in Cohort A and 40% of patients treated in Cohort B. Median survival in Cohort A and Cohort B were 2.3 months and 4.3 months respectively in a patient population that had received > 2 prior chemotherapies. This compares well with what is reported for first and second line therapy in this patient population. Fourth, mesothelin-specific T cell responses have been observed in treated patients. Interestingly, unlike patients with resected cancer, mesothelin-specific T cell responses can be detected at baseline, prior to vaccination, in patients with metastatic pancreatic cancer. In addition, there was a trend toward prolonged progression-free survival in those patients who demonstrated persistent mesothelin-specific T cell responses with therapy. These data would suggest that even in metastatic patients, tumor-specific T cells can be detected.

This study represents the first demonstration that integrating immunomodulatory doses of Cy with a GM-CSF-secreting vaccine in patients with advanced pancreatic cancer is safe and feasible to administer. These data suggest that the vaccine given in sequence with Cy results in anti-tumor activity that is at least similar to GEM containing chemotherapy. In addition, mesothelin-specific $CD8^+$ T cell responses can be detected in stage 4 patients treated with the vaccine and may correlate with time to progression and overall survival. Thus, these findings provide the scientific

rationale to continue to test combinations of vaccine with other more potent immune modifying agents.

2.4 Rationale

Barriers to effective immunotherapy strategies against pancreatic adenocarcinoma (PDA) include a multitude of immune tolerance mechanisms both at the systemic level and in the tumor microenvironment. Combinatorial strategies aimed at priming tumor antigen-specific T cells while simultaneously blocking negative immune checkpoints will be necessary to show an effect in PDA. There is increasing interest in the role of immunotherapy in the treatment of cancers. Ipilimumab (IPI, Yervoy), is an antagonist antibody to cytotoxic T-lymphocyte antigen-4 (CTLA-4) which down-regulates T cell activation. IPI as single agent was approved for the treatment of metastatic melanoma based on a 3.7 month improvement in overall survival (OS) (Hodi, *et al*, 2010). Similarly, based on a 4.1 month survival benefit, Provenge vaccine has been approved for prostate cancer (Kantoff, *et al*, 2010). Another immune checkpoint blocker, anti-programmed death-1 (PD-1), is showing promising results in melanoma, renal cell, and lung cancer (Topalian, *et al*, 2012). Despite excitement over these new agents, cancers like PDA are unlikely to respond to single agent therapy. Unlike melanoma, few tumor infiltrating lymphocytes naturally develop in PDA, so that these agents have nothing to target. Thus, vaccines are necessary to prime and expand tumor specific T cells at the time that these T cell activating agents are administered to cause PDA regression.

Pancreatic Tumor Vaccine Induces Antigen-Specific T Cells. The use of whole-cell vaccines is promising because it delivers a range of antigens without the need for specific knowledge of the relevant target antigens (Dranoff, *et al*, 1993). The vaccine consists of 2 allogeneic pancreatic tumor cell lines (Panc 6.03 and Panc 10.05) that have been modified with a plasmid vector encoding the cDNA for human granulocyte macrophage-colony stimulating factor (GM-CSF) and subsequently cultured and irradiated. The GM-CSF simultaneously recruits and provides maturation signals to antigen-presenting cells (APC) to the local vaccine site. APCs then orchestrate the immune response by processing the tumor antigens and presenting them to effector cells. A number of studies have been completed and are underway using the vaccine in the treatment of PDA (Jaffee, *et al*, 2001; Laheru, *et al*, 2008; Lutz, *et al*, 2011). The prior studies demonstrate that the vaccine is safe and that induction of T cell responses to the tumor antigen, mesothelin, correlates with survival. For the purposes of this proposal, two of the most recent studies will be highlighted. In an ongoing neoadjuvant study, the vaccine is given either alone or in combination with low dose cyclophosphamide (CY). CY targets a population of regulatory T cells (Tregs) that inhibit tumor-specific T cell responses. We have been able to demonstrate the influx of immune cells and formation of lymphoid aggregates within the tumor in a majority of patients. We believe that for PDA, a vaccine is critically important to prime T cells that can then migrate to the tumor. Without the vaccine, pancreatic tumors lack significant inflammation and the T cells that exist are primarily Tregs. In the neoadjuvant study, the vaccine is able to induce an influx of tumor infiltrating lymphocytes as early as 2 weeks after vaccine administration.

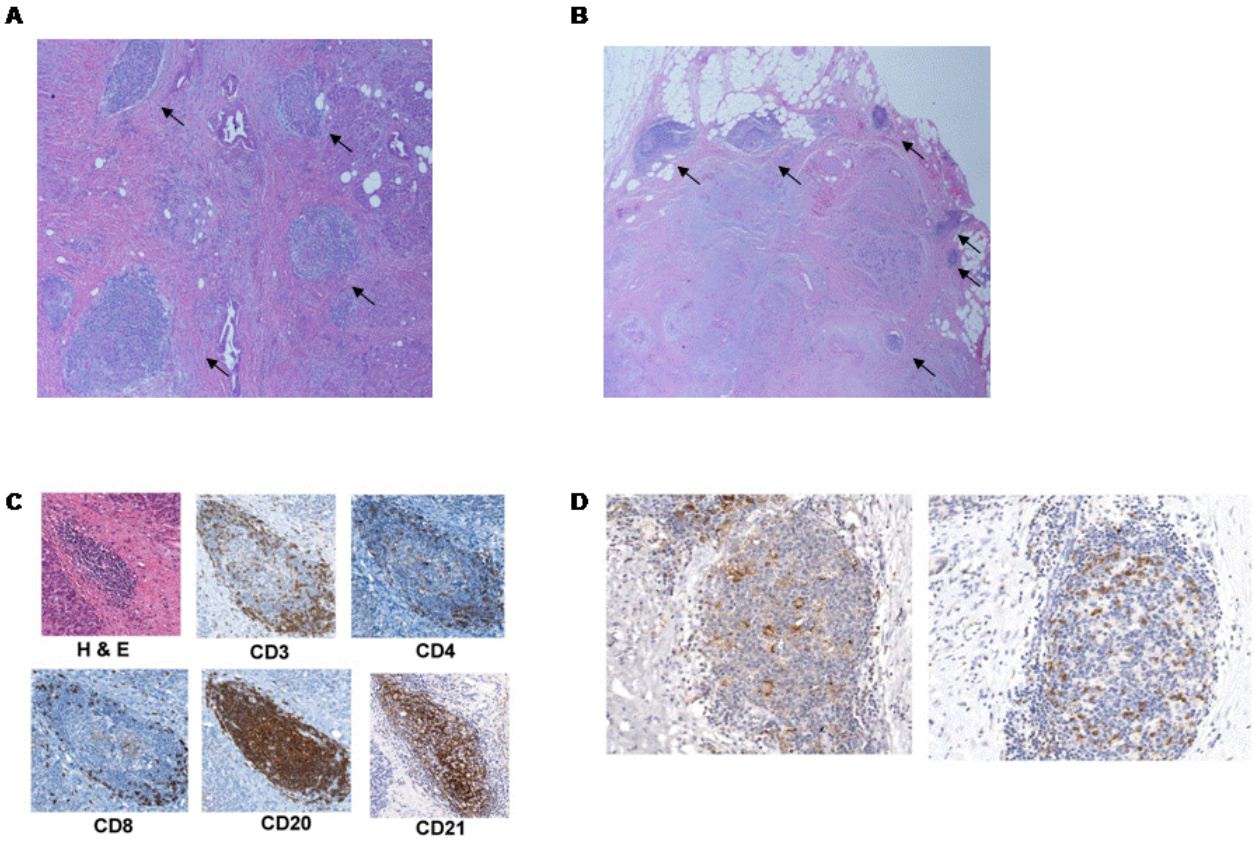


Figure 1. Pancreatic Tumor Vaccine induces lymphoid aggregates in pancreatic tumors. **A.** Lymphoid aggregates (arrows) were found in intratumoral locations of PDAs 2 weeks after vaccination. **B**. Lymphoid aggregates (arrows) were found in peritumoral locations of PDAs from vaccinated patients. **C.** Immunohistochemistry (IHC) staining of a representative lymphoid aggregate. Hematoxylin and eosin (H&E), anti-CD3, CD4, CD8 staining of T cells, anti-CD20 staining of B cells, and anti-CD21 staining follicular dendritic cells, a hallmark of germinal centers. **D.** IHC staining demonstrates PD-L1 (left panel) staining on tumors and monocytes and PD-1 (right panel) staining on T cells within the same lymphoid aggregate.

Figure 1 is an example of a resected tumor with lymphoid aggregates consisting of a number of cell types including B and T cells (1A-C). Upregulation of another important immune checkpoint pathway (PD-L1/PD-1) is also apparent (1D). These lymphoid aggregates were seen in the majority of vaccinated patients but the number of aggregates range from 1-35/HPF. While the vaccine is able to generate tumor infiltrating lymphocytes, preclinical studies suggest that combinatorial strategies will be necessary in difficult to treat tumors. One strategy is to combine vaccines with immune checkpoint inhibitors such as anti-CTLA-4, anti-PD-1, and anti-PD-L1. In fact, the immune checkpoint inhibitors can release the brakes on vaccine-induced T cells. Concurrent administration of CTLA-4 antibody and GM-CSF-secreting tumor cells is synergistic in several mouse models (B16 melanoma, SM1 mammary carcinoma, and TRAMP prostate carcinoma) (Van Elsa, *et al*, 1999; Hurwitz, *et al*, 1998; Hurwitz, *et al,* 2000).

Studies combining IPI with both prostate tumor vaccine and pancreatic tumor vaccine have been completed (van den Eertwegh, et al, 2012). Despite being performed in heavily pre-treated patients, both studies showed both CT scan regressions and tumor marker declines. Twenty-five percent of men with prostate cancer had PSA responses and 2 men at the higher dose levels showed regressions on imaging. The study in PDA is described below.

Phase 1b Ipilimumab versus Pancreatic Tumor Vaccine + Ipilimumab in Advanced Pancreatic Cancer. Thirty patients with previously treated PDA were randomized 1:1 to IPI at 10mg/kg alone (arm 1) or in combination with vaccine (arm 2). The higher dose of 10mg/kg of IPI was chosen because IPI at 3mg/kg in PDA had previously been reported and demonstrated a low but detectable response rate. Studies in melanoma also suggested that the 10mg/kg dose was more efficacious. Patients received 4 induction doses of IPI or Vaccine/IPI at 3-week intervals and then maintenance with the same treatment every 3 months.

Baseline Characteristics and Safety. Baseline characteristics were similar among patients in each arm with the exception that arm 1 had fewer patients with $\geq$ 2 prior therapies (60 vs 100%, p=0.017). The most common adverse event (AE) reported for IPI therapy were immune-related adverse events (IRAE); the most common AEs reported for GM-CSF secreting vaccines were localized vaccine reactions and self-limiting systemic rashes. The rate of IRAEs (e.g. colitis, hypophysitis) attributable to IPI was similar to what has been reported in other studies testing IPI at the 10mg/kg dose. Twenty percent of patients in both arms experienced Grade 3-4 IRAEs. Similar to other IPI studies, a majority of patients responded to steroid treatment.

Anti-tumor Activity. The best RECIST response was stable disease (SD) in two patients in arm 1 and two patients in arm 2. Using the immune-related RECIST criteria (irRC), arm 2 had an additional patient with SD for 81 weeks. Immune-related response criteria (irRC) account for the kinetics of both old and new lesions given the known for potential delayed responses with IPI. The quality of the responses in the two arms was different. Patients with SD on arm 1 had continuous disease progression that did not reach the 20% growth cutoff for 7 and 22 weeks. Arm 2 had three SD (1 regression starting at week 14 and maintained until week 31, one stabilization starting at week 22 and continued for 81 weeks, one SD continued for 71+ weeks). **Figure 2A-C** demonstrates CT findings of early tumor progression followed by regression starting at week 14 and the corresponding CA19-9 responses (**Figure 2D**). This patient lived 12 months. **Figure 2E** demonstrates interesting CA19-9 kinetics in a patient who had stable local disease which continued for 71+ weeks. The baseline elevated CA 19-9 increased further during high dose steroid treatment of hypophysitis and then showed a gradual delayed normalization. This patient lived 31 months. **Figure 2F** shows the CA 19-9 kinetics of a patient with early local progression and a new omental lesion at week 7 followed by disease stabilization starting at week 22 and lasting until week 81. The CA19-9 rise between the 12 week maintenance doses declined in response to treatments. This patient is still alive and current survival is 30+ months. CA19-9 declines in association with Vaccine + IPI treatment were seen for 7/15 patients. In contrast, 0/15 patients receiving IPI alone had CA19-9 declines. Median overall survival (OS) was 3.7 months (95% CI: 2.5 to 9.2) for arm 1 and 5.7 months (95% CI: 4.3 to 14.7) for arm 2 (HR: 0.51, 95% CI: 0.23 to 1.08, p=0.072). The percent alive after one year also favored the combination arm (7% vs 27%) (**Figure 2G**).

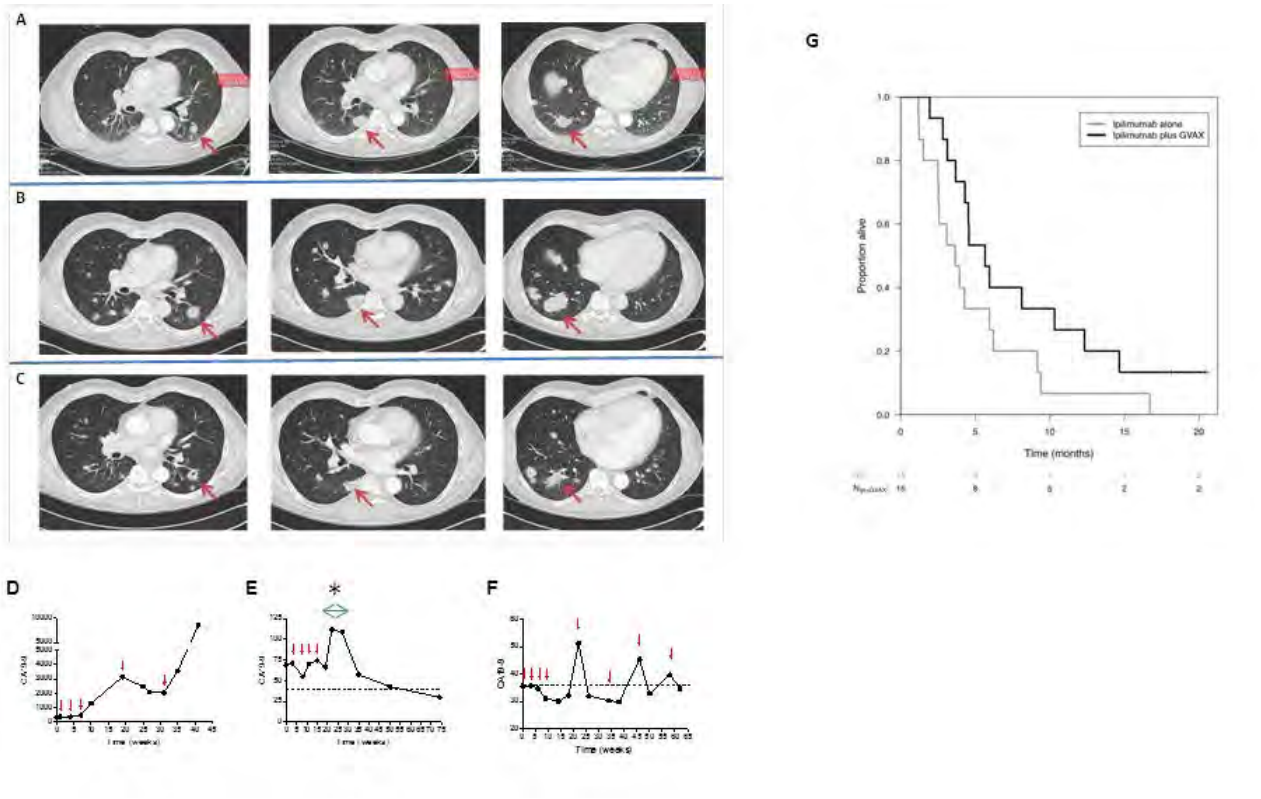


Figure 2.Clinical responses to Pancreatic Tumor Vaccine + Ipilimumab. A) Baseline scan. B) Week 7 scan shows growth from baseline. C) Week 14 scan shows minor response maintained until week 31. D) CA 19-9 responses paralleled clinical response in the same patient. Small arrows denote treatment administration. E) Delayed CA 19-9 response in a patient who received steroids (*) for hypophysitis. F) Patient with localized disease that was progressive on CT at week 7 (local progression and new omental lesion) and 14 and then SD from week 22 to 81. G) KM overall survival curve as of 1/15/2012. One patient in Vaccine + IPI is alive as of 12/12/2012.

2.5 Correlative Studies Background

Mesothelin-specific T cell responses. We also demonstrated that tumor antigen-specific T cells could be elicited in a metastatic patient population. Enhanced post-vaccination mesothelin-specific T cell responses were associated with increased disease-free survival (DFS) and OS in prior pancreatic tumor vaccine studies (Jaffee, *et al*, 2001; Thomas, *et al*, 2004; Laheru, *et al*, 2008; Lutz, *et al*, 2011). Mesothelin-specific T cell responses were analyzed in peripheral blood lymphocytes (PBL) from 19 patients with at least one post-treatment PBL sample. Baseline, post-treatment 1, and peak-induction T cell responses are shown in **Figure 3A** as a correlate of OS for the combined treatment arms. Although mesothelin-specific T cell responses were not enhanced following the first treatment in either group, there was a significant induction of peak post-treatment responses among patients with OS > 4.3 months (p=0.014). Mesothelin-specific T cell responses were measured following 2 or more treatments in 14 of the 19 patients and are shown in **Figure 3B**. Similar to the analysis for all 19 patients evaluated, T cell responses were not enhanced following the first treatment for either group, and peak post-treatment responses were enhanced only in patients with OS > 4.3 months (p=0.020) and remained elevated throughout treatment, albeit not significantly (p=0.13). The size of the mesothelin-specific T cell repertoire measured

following the first and final treatments in these 14 patients are shown in **Figure 4A**. T cell repertoire size was similar following the initial treatment, but significantly larger following multiple treatments among patients with OS > 4.3 months (p=0.009). Furthermore, expansion in the repertoire was observed in six of nine patients with OS > 4.3 months but not in any of the five patients with OS ≤ 4.3 months (**Figure 4B**) and was associated with longer OS (p=0.031).

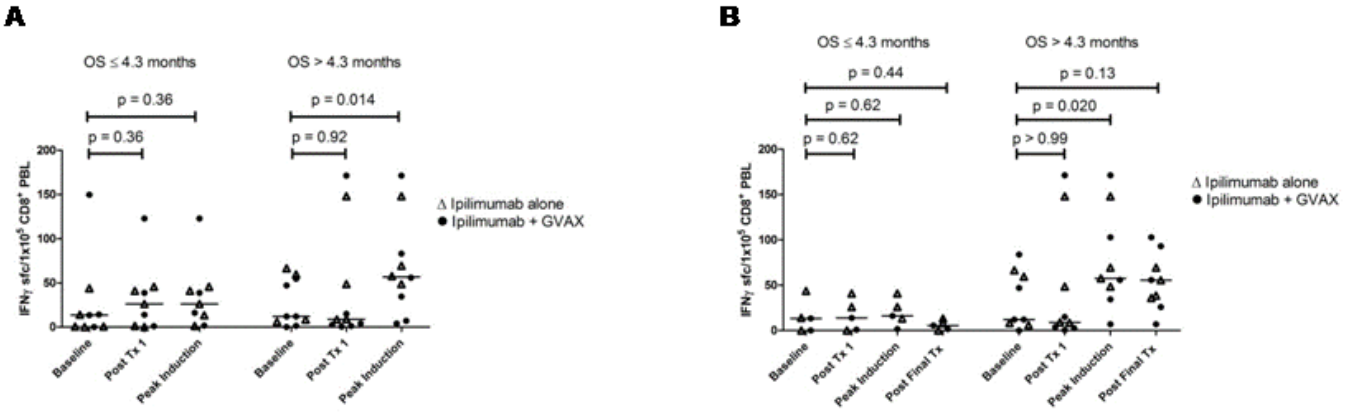


Figure 3.Longer survival is associated with an induction of CD8$^+$mesothelin-specific T cell responses. Mesothelin peptide-specific CD8$^+$ T cells were quantitated in pre- and post-treatment PBL using IFNγ ELISPOT assays. **A**) Mesothelin-specific T cell frequencies measured at baseline, following the first treatment, and at the peak of induction in 19 HLA-A1$^+$ and/or HLA-A2$^+$ patients receiving at least one treatment. **B**) Mesothelin-specific T cell frequencies measured at baseline, following the first treatment, at the peak of induction, and following the final treatment in 14 of the 19 patients who received at least two treatments. Patients in both treatment arms (Ipilimumab alone = open triangles; Ipilimumab + Vaccine = solid circles) were grouped together based on survival of greater than or less than 4.3 months. Post-treatment T cell levels were compared to baseline levels using Wilcoxon sign-rank tests.

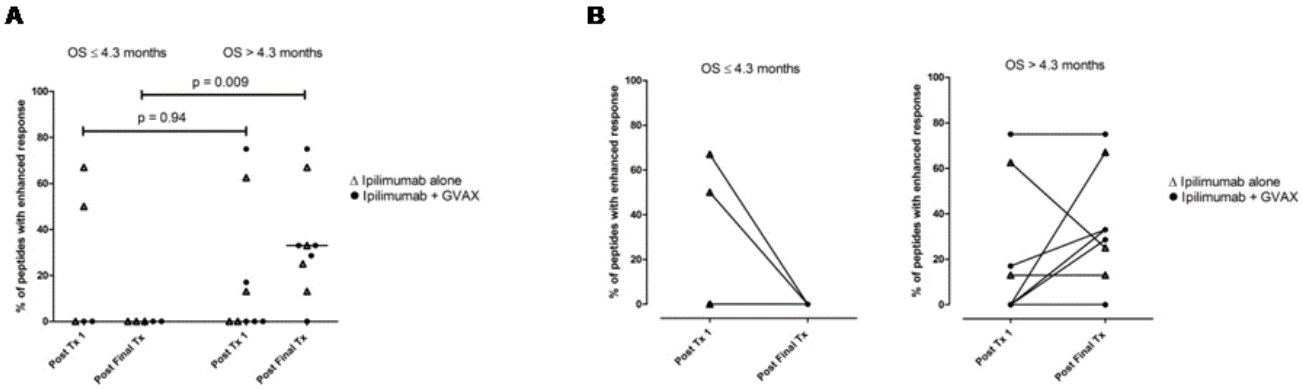


Figure 4. Longer survival is associated with post-treatment expansion of the mesothelin-specific CD8$^+$ T cell repertoire. The percentage of mesothelin peptides for which enhanced T cell responses were measured following the first (Post Tx1) and final treatments (Post Final Tx) are shown for 14 patients receiving two or more treatments with Ipilimumab alone (open triangles) or Ipilimumab + Vaccine (solid circles). **A**) T cell repertoires in patients grouped based on survival of less than or greater than 4.3 months. Comparisons between group T cell repertoires were made using Mann Whitney tests. **B**) Changes in mesothelin-specific T cell repertoires in patients surviving 4.3 months or less (left) and greater than 4.3 months (right).

This is the first study to evaluate IPI-induced mesothelin-specific T cell responses either alone or in combination with a vaccine. Indeed, mesothelin-specific T cell responses were measured in patients following treatment with IPI alone and with the combination. T cell responses measured in both arms were analyzed together because the pattern of induction and association with survival were similar between the two arms and also because of the small sample size. The induction of mesothelin responses in the IPI alone arm support the concept that non-antigen-specific agents such as IPI act by enhancing pre-existing endogenous tumor-specific T cells. Interestingly, diversification of the mesothelin-specific T cell repertoire with additional treatments was seen in both arms. However, a greater number of patients in the combination arm exhibited these responses (4/7) compared to the IPI alone arm (2/7) suggesting that the frequency of pre-existing mesothelin-specific T cells are low and require a vaccine to induce larger pools of precursor T cells. Consistent with a prior study, post-treatment expansion of the mesothelin-specific T cell repertoire was associated with longer OS. In this study, median survival for the six patients demonstrating an expansion in their mesothelin-specific T cell repertoires was 15.7 months compared to 4.1 months for the 8 patients whose repertoires were unchanged following treatment.

Serum markers of response. Unique to the vaccine arm was the induction of galectin-3 (gal-3) antibody responses. Gal-3 was previously identified on a proteomics screen using immunized sera from patients vaccinated with the PDA vaccine. Gal-3 is expressed by dendritic cells, regulatory T cells, and tumors and plays a role in T cell apoptosis and tolerance (Shimamura, *et al*, 2002; Peng, *et al*, 2008; Hsu, *et al*, 2009; Chen, *et al*, 2009). Induction of gal-3 antibody responses was limited to arm 2 (**Figure 6**). While patients whom maintained a titer of $\geq$ 0.10 for at least 2 time-points, survived longer than those who did not, it remains to be seen if maintenance of titers is actually protective. Nonetheless, the differential antibody responses between the two arms may provide clues as to how mechanistically these treatments may differ. The pancreatic tumor vaccine can induce both humoral and T cell responses. Proteomics screens using pre and post treatment sera are underway to identify potential therapeutic targets as well as biomarkers of response and autoimmune toxicity.

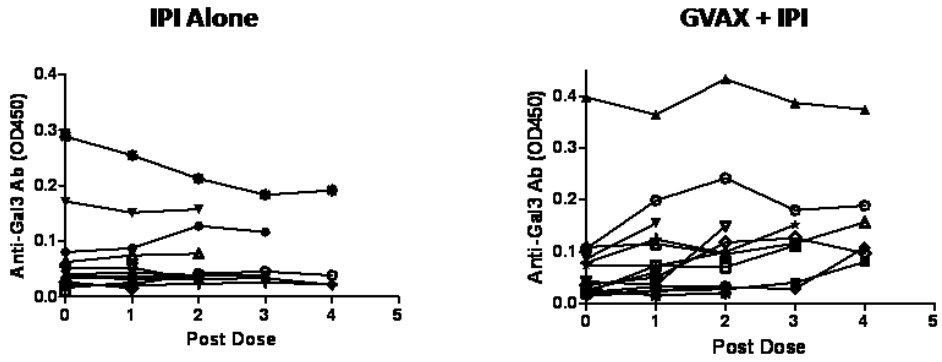


Figure 6. Galectin-3 antibody responses were induced only in the Vaccine + IPI arm.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Have histologically proven adenocarcinoma of the pancreas. Patients with mixed histology will be excluded.

3.1.2 Have stable metastatic pancreatic cancer after receiving 8-12 doses of FOLFIRINOX (measurable disease is not required).

3.1.3 Be at least 18 years of age.

3.1.4 Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (Karnofsky >60%, see **Appendix B**).

3.1.5 Life expectancy of greater than 3 months.

3.1.6 Patients must have normal organ and marrow function as defined below:

- WBC $\geq$3500/uL
- ANC $\geq$1500/uL

- Platelets $\geq 90 \times 10^3$/uL
- Hemoglobin ≥ 9 g/dL
- Total bilirubin ≤1.5 x ULN
- AST(SGOT)/ALT(SGPT) ≤2.5 x ULN(≤ 5 x ULN for patients with documented liver metastases)
- Creatinine ≤ 2.0 x ULN

3.1.7 The effects of Ipilimumab and the Pancreatic Tumor Vaccine on the developing human fetus are unknown. For this reason women of child-bearing potential (WOCBP) and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea ≥ 12 consecutive months; or women on hormone replacement therapy [HRT] with documented serum follicle stimulating hormone [FSH] level > 35 mIU/mL). Even women who are using oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy, or are practicing abstinence or where their partner is sterile (eg, vasectomy) should be considered to be of childbearing potential.

3.1.8 Ability to understand and the willingness to sign a written informed consent document.

3.1.9 Oxygen saturation on room air > 92 % by pulse oximetry. (Patients on intermittent or continuous supplemental oxygen are not allowed).

3.2 Exclusion Criteria

3.2.1 Patients in whom histologic diagnosis is not consistent with ductal adenocarcinoma such as adenosquamous, squamous cell, colloid, islet cell, serous or mucinous cystadenoma or cystadenocarcinoma, carcinoid, small or large cell carcinoma, intraductal oncocytic papillary neoplasms (IOPN), osteoclast-like giant cell tumors, acinar cell carcinoma, pancreatoblastoma, solid pseudopapillary tumors, undifferentiated small cell carcinoma and non-epithelial tumors (sarcomas, GI stromal tumor, lymphoma).

3.2.2 Patients who have adenocarcinomas of the ampulla, distal bile duct, and duodenum.

3.2.3 Patients who have had surgery within 4 weeks of dosing of investigational agent, excluding minor procedures (dental work, skin biopsy, etc), celiac plexus block, and biliary stent placement.

3.2.4 Patients who have been off of FOLFIRINOX more than 70 days prior to treatment on study.

3.2.5 Patients who have had prior chemotherapy for metastatic pancreatic cancer (other than FOLFIRINOX). Prior radiation is allowed. Chemotherapy for non-metastatic disease is allowed.

3.2.6 Patients with a history of prior treatment with ipilimumab, anti-PD 1 antibody, CD137 agonist or anti-CD 40 antibody.

3.2.7 Patients who have received any non-oncology live vaccine therapy used for prevention of infectious diseases (for up to one month prior to or after any dose of ipilimumab/vaccine).

3.2.8 Patients who are receiving any other investigational agents.

3.2.9 Patients who have received any of the following concomitant therapy: IL-2, interferon, immunosuppressive agents, or chronic use of systemic corticosteroids (used in the management of cancer or non-cancer-related illnesses).

3.2.10 Autoimmune disease: Patients with a history of inflammatory bowel disease, including ulcerative colitis and Crohn's Disease, are excluded from this study, as are patients with a history of symptomatic disease (*e.g.*, rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, autoimmune vasculitis [*e.g.*, Wegener's Granulomatosis]); CNS or motor neuropathy considered of autoimmune origin (*e.g.*, Guillain-Barre Syndrome and Myasthenia Gravis, multiple sclerosis). Patients with thyroid disease will be allowed. Autoimmune diagnoses not listed here must be approved by the protocol chair, following discussion with the study sponsor and CTEP.

3.2.11 Patients with known immune impairment who may be unable to respond to anti-CTLA 4 antibody.

3.2.12 Patients with known brain metastases should be excluded from early clinical trials because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

3.2.13 Patients with radiographic ascites that is apparent on physical exam or requiring medical intervention (medication or procedures) in the 2 months prior to enrollment.

3.2.14 Patients with uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements or obscure the interpretation of AEs.

3.2.15 Patients with a known or suspected hypersensitivity to GM-CSF, hetastarch, corn, DMSO, fetal bovine serum, or trypsin (porcine origin).

3.2.16 Patients with chronic HIV, Hepatitis B or hepatitis C infections should be excluded because of potential effects on immune function and/ or drug interactions.

3.2.17 WOCBP who are unwilling or unable to use an acceptable method to avoid pregnancy for the entire study period and for up to 8 weeks after the last dose of investigational product.

3.2.18 Women who are pregnant or breastfeeding.

3.2.19 Women with a positive pregnancy test on enrollment or prior to investigational product administration.

3.2.20 Sexually active fertile men not using effective birth control if their partners are WOCBP.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 General Guidelines

Eligible patients will be entered on study centrally at the Sidney Kimmel Comprehensive Cancer Center at the Johns Hopkins University by the Study Coordinator. All sites should call the Study Coordinator at [redacted] or [redacted] to verify drug availabilities. The fax cover sheet, Registration Form, and Eligibility Worksheet will be provided to the additional site.

Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO [redacted]

4.2 Registration Process

To register a patient, the following documents should be completed by the Research Nurse or Study Coordinator and faxed [redacted] to the Study Coordinator:

- Fax cover sheet
- Registration Form
- Signed patient consent form
- HIPAA authorization form
- Eligibility Screening Checklist
- Copy of required screening tests

The Research Nurse or Study Coordinator at the participating site will then call [redacted] the Study Coordinator to verify eligibility. To complete the registration process, the Study Coordinator will:

- Assign a patient study number
- Register the patient on the study
- Fax or e-mail the patient study number to the participating site
- Call the research nurse or data manager at the participating site and verbally confirm registration.

4.3 Randomization Process

Patients will be randomized to Arm A (ipilimumab + vaccine) or Arm B (FOLFIRINOX) in a 1:1 fashion using a randomized block design. Patients who are randomized will be considered in the final analysis.

5. TREATMENT PLAN

5.1 Agent Administration

Treatment will be administered on an outpatient basis. Appropriate dose modifications are described in **Section 6**. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Regimen Description Arm A

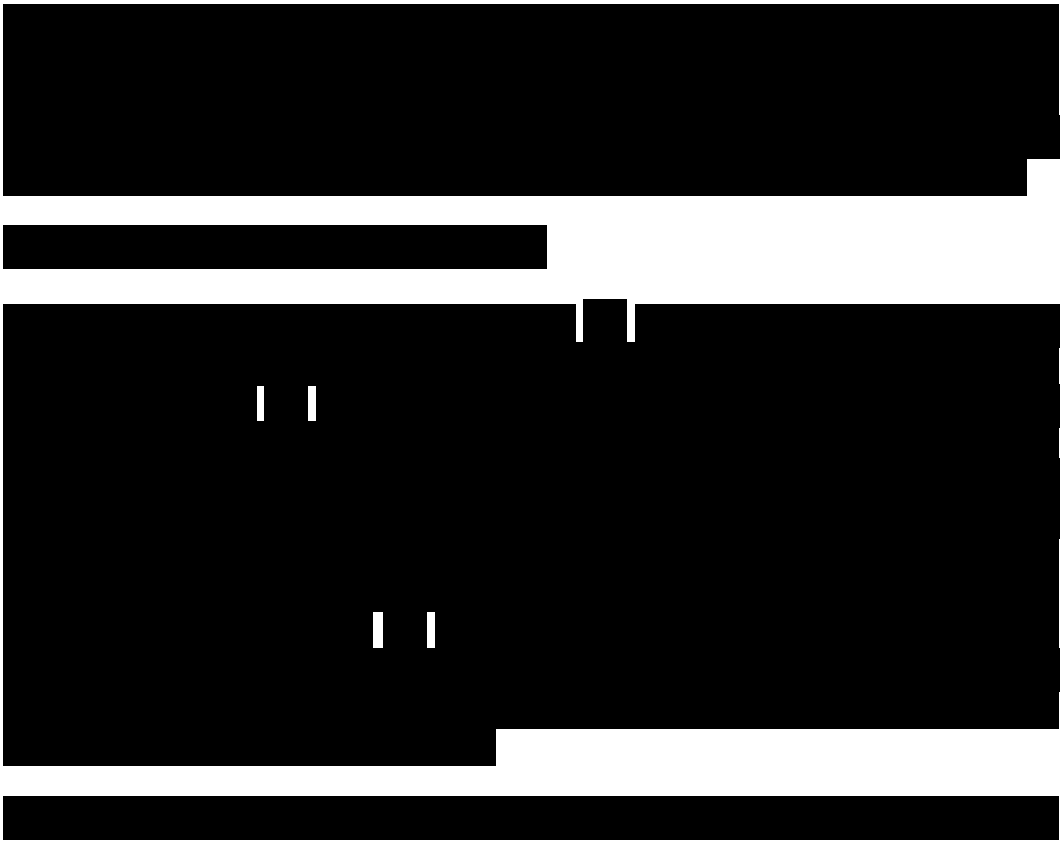
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***
Pancreatic Tumor Vaccine	EMLA cream (approximately 2.5 grams per site, at least 1 hour prior to vaccination)	$5x10^8$ cells in approximately (six syringes)	Six intradermal injections	Every 3 weeks for 4 doses, then every 8 weeks

Ipilimumab	Premedication with 50 mg diphenhydramine at discretion of PI	3 mg/kg in NS (10 mg/kg for patients starting treatment prior to protocol v6.0 approval)	IV infusion over 90 min	

Regimen Description Arm A Patients That Must Discontinue Ipilimumab Due to Toxicity

Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***
Cyclophosphamide (Day 1)	Patients may be pre-medicated prior to administration with anti-emetics.	200 mg/m^2 in 100ml NS	IV infusion over 30 min	Every 3 weeks for 4 doses, then every 8 weeks
Pancreatic Tumor Vaccine (Day 2)	EMLA cream (approximately 2.5 grams per site, at least 1 hour prior to vaccination)	5x10^8 cells in approximately (six syringes)	Six intradermal injections	

5.1.1 Allogeneic GM-CSF Transfected Pancreatic Tumor Vaccine



[redacted]

[redacted]

[redacted]

5.1.2 Ipilimumab

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.1.3 FOLFIRINOX

Patients on Arm B would have already been receiving FOLFIRINOX as standard of care and dose modifications should be made according to the patient's known tolerability.

5.2 Prohibited and Restricted Therapies

Patients in Arm B of this study may use standard vaccines. Where possible, routine vaccination for influenza, pneumoccal pneumonia should be given prior to the start of therapy but may be administered during treatment when clinically indicated. Vaccination should be given when there is enough separation to distinguish any vaccine reactions from drug toxicity. There is no experience using live attenuated vaccination during ipilimumab therapy, therefore administration of live vaccine is not allowed for patients in Arm A of this study during treatment.

Concomitant systemic or local anti-cancer medications or treatments are prohibited in this study while receiving ipilimumab treatments.

Patients may not use any of the following therapies during the study:

- Any non-study anti-cancer agent (investigational or non-investigational)
- Any other investigational agents
- Any other CTLA-4 inhibitors or agonists
- CD137 or other immunologic activation agonists
- Immunosuppressive agents (on the vaccine arm)
- Chronic systemic corticosteroids (on the vaccine arm)
- Granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), or erythropoietin (on the vaccine arm).

5.3 General Concomitant Medication and Supportive Care Guidelines

5.3.1 Ipilimumab

5.3.1.1 Immune-Related Adverse Events (IRAEs): Definition, Monitoring, Treatment

Blocking CTLA-4 function may permit the emergence of auto-reactive T cells and resultant clinical autoimmunity. Rash/vitiligo, diarrhea/colitis, uveitis/episcleritis, hepatitis and hypopituitarism were drug-related, presumptive autoimmune events, now termed IRAEs, noted in previous ipilimumab studies.

For the purposes of this study, an IRAE is defined as an AE of unknown etiology, associated with drug exposure and is consistent with an immune phenomenon. Efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic

causes prior to labeling an AE an IRAE. Serological, immunological, and histological (biopsy) data should be used to support the diagnosis of an immune-mediated toxicity. Suspected IRAEs must be documented on an AE or SAE CRF.

Patients should be informed of and carefully monitored for evidence of clinically significant systemic IRAE (e.g., systemic lupus erythematosus-like diseases) or organ-specific IRAE (e.g., rash, colitis, uveitis, hepatitis or thyroid disease). If an IRAE is noted, appropriate work-up (including biopsy if possible) should be performed, and steroid therapy may be considered if clinically necessary (see **Appendix C** for suggested work-up and treatment of IRAEs).

It is unknown if systemic corticosteroid therapy has an attenuating effect on ipilimumab activity. However, clinical anti-tumor responses have been maintained in patients treated with corticosteroids and discontinued from ipilimumab. If utilized, corticosteroid therapy should be individualized for each patient. Prior experience suggests that colitis manifested as ≥ Grade 3 diarrhea requires corticosteroid treatment. See **Appendix C** for additional details.

5.3.1.2 Infusion Reactions Associated with Ipilimumab

Since ipilimumab contains only human protein sequences, it is less likely that any allergic reaction will be seen in patients. However, it is possible that infusion of ipilimumab will induce a cytokine release syndrome that could be evidenced by fever, chills, rigors, rash, pruritus, hypo- or hypertension, bronchospasm or other symptoms. No prophylactic pre-medication will be given unless indicated by previous experience in an individual patient.

Reactions should be treated based upon the following recommendations:

For mild infusion-related symptoms (e.g., localized cutaneous reactions such as mild pruritus, flushing, rash) or CTC Grade 1 allergic reactions (transient flushing or rash, drug fever< 38°C):

- Decrease the rate of infusion until recovery from symptoms, remain at bedside and monitor patient;
- Complete the ipilimumab infusion at the initial planned rate ;
- Diphenhydramine 50 mg IV may be administered at the discretion of the treating physician and patients may receive additional doses with close monitoring;
- Premedication with diphenhydramine may be given at the discretion of the Investigator.

For moderate infusion-related symptoms (any symptom not listed above [mild symptoms] or below [severe symptoms] such as generalized pruritus, flushing, rash, dyspnea, hypotension with systolic BP > 80 mmHg) or CTC Grade 2 allergic reactions (generalized rash, flushing, urticaria, dyspnea, drug fever≥ 38°C):

- Interrupt ipilimumab;

- Administer diphenhydramine 50 mg IV;
- Monitor patient closely until resolution of symptoms;
- Corticosteroids may abrogate any beneficial immunologic effect, but may be administered at the discretion of the treating physician;
- Resume ipilimumab infusion after recovery of symptoms;
- At the discretion of the treating physician, ipilimumab infusion maybe resumed at one half the initial infusion rate, then increased incrementally to the initial infusion rate.
- If symptoms develop after resumption of the infusion, the infusion should be discontinued and no additional ipilimumab should be administered that day;
- The next dose of ipilimumab will be administered at its next scheduled time and may be given with pre-medication (diphenhydramine and acetaminophen) and careful monitoring, following the same treatment guidelines outlined above;
- At the discretion of the treating physician additional oral or IV antihistamine may be administered prior to dosing with ipilimumab.

For severe infusion-related symptoms (e.g., any reaction such as bronchospasm, systolic blood pressure < 80 mm Hg, or angioedema) or CTC Grade 3 or 4 allergic reactions (symptomatic bronchospasm, angioedema, hypotension):

- Immediately discontinue infusion of ipilimumab, and disconnect infusion tubing from the subject;
- Consider bronchodilators, epinephrine 0.3 - 0.5 mg IM (0.3 ml-0.5 ml of 1:1000 solution), and/or diphenhydramine 50 mg IV, with solumedrol 100 mg IV, as needed.
- Patients should be monitored until the Investigator is comfortable that the symptoms will not recur;
- No further ipilimumab will be administered;

In case of late-occurring hypersensitivity symptoms (e.g., appearance within one week after treatment of a localized or generalized pruritus), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).

5.3.1.3 Treatment of Ipilimumab Related Isolated Drug Fever

In the event of isolated drug fever, the Investigator must use clinical judgment to determine if the fever is related to the ipilimumab or to an infectious etiology.
If a patient experiences isolated drug fever, for the next dose, pre-treatment with acetaminophen should be instituted and a repeated antipyretic dose at 6 and 12 hours after ipilimumab infusion, should be administered. The infusion rate will remain unchanged for future doses.
If a patient experiences recurrent isolated drug fever following premedication and post dosing with an appropriate antipyretic, the infusion rate for subsequent dosing

should be decreased to 50% of the previous rate. If fever recurs following infusion rate change, the Investigator should assess the patient's level of discomfort with the event and use clinical judgment to determine if the patient should receive further ipilimumab.

5.3.2 Allogeneic GM-CSF Transfected Pancreatic Tumor Vaccine

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.

5.3.3 FOLFIRINOX

General concomitant medication and supportive care guidelines for FOLFIRINOX are recommendations and at the discretion of the treating physician.

5.3.3.1 Anti-emetics

Patients should be pre-medicated prior to the FOLFIRINOX treatment with anti-emetics per institutional guidelines. Agents that may be considered include, but are not limited to: promethazine, prochlorperazine, metoclopramide, haloperidol, droperidol, lorazepam and serotonin-antagonists (e.g. ondansetron, granisetron, dolasetron).

Delayed emesis, should it occur, will be treated for future FOLFIRINOX chemotherapy doses with a delayed emesis regimen.

Due to the emetogenic nature of this regimen, aprepitant will be administered with each cycle in addition to concomitant anti-emetics at the discretion of the treating physician.

5.3.3.2 Anti-diarrheal

Loperamide: For symptoms of diarrhea and/or abdominal cramping that occur at any time during a treatment cycle patients will be instructed to begin taking loperamide. Loperamide should be started at the earliest sign of (1) a poorly formed or loose stool or (2) the occurrence of 1 to 2 more bowel movements than usual in 1 day or (3) an increase in stool volume or liquidity. Loperamide should be taken in the following

manner: 4 mg at the first onset of diarrhea, then 2 mg every 2 hours around the clock until diarrhea-free for at least 12 hours. Patients may take loperamide 4 mg every 4 hours during the night. The maximum daily dose of loperamide is 16 mg/day.

Antibiotics: Oral fluoroquinolone treatment may be initiated for ANC<500 or diarrhea for >24 hours despite loperamide, at the discretion of the treating physician.

5.3.3.3 Anticoagulants

Prophylactic or therapeutic doses of Coumadin or low-molecular weight heparin are permitted.

Low-dose aspirin (≤ 325 mg/d): Aspirin may be continued if the patient was on this prior to enrollment.

5.3.3.4 Growth Factors

Peg-filgrastim (Neulasta) will be administered 24-72 hours after each dose (every 2 weeks or as clinically indicated) at the discretion of the treating physician.

The use of erytropoetin EPO in this protocol is permitted at the discretion of the treating physician. However, these agents are not recommended.

5.4 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue indefinitely or until one of the following criteria applies:

- Clinically significant disease progression (**Section 5.6**).
- Intercurrent illness that prevents further administration of treatment,
- Pregnancy
- Unacceptable adverse event(s) requiring temporary or permanent stopping of study drug (see also **Section 6**).
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.
- Termination of the study by Bristol-Myers Squibb (BMS), CTEP, or the sponsor.

5.5 Duration of Follow Up

All patients will be followed for survival status by telephone, email, clinic visit, or by collection of outside records once off study. Contact will occur approximately every 12 weeks (or until study termination) to evaluate OS, PD, subsequent cancer therapies, and AEs. Adverse events 70 days after the last dose of investigational agent (Arm A) will only be recorded if deemed possibly, probably, or definitely related to the investigational agent. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. Any patients that have received the pancreatic tumor vaccine (Arm A) will also have annual evaluations (+/- 2 months) either at Hopkins or locally until study termination. If consent is granted, patients who received vaccine will continue to be followed annually after study termination via a separate protocol entitled "Long-term follow-up of patients who receive lethally irradiated allogeneic pancreatic tumor cells transfected with the GM-CSF gene." Consent for this long-term follow up may be obtained at any point in the protocol.

5.6 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in **Section 5.4** applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

Alternative criteria for continuing treatment during progression are provided.

Ipilimumab is expected to trigger immune-mediated responses, which require activation of the immune system prior to the observation of clinical responses. Such immune activation may take weeks to months to be evident. Some patients may have objective volume increase of tumor lesions or other disease parameters (based on study indication, i.e., hematologic malignancies) within (specific 12-24) weeks following the start of ipilimumab dosing. Such patients may not have had sufficient time to develop the required immune activation or, in some patients, tumor volume or other disease parameter increases may represent infiltration of lymphocytes into the original tumor or blood. In conventional studies, such tumor volume or relevant laboratory parameter increases during the first 12 weeks of the study would constitute PD and lead to discontinuation of imaging to detect response, thus disregarding the potential for subsequent immune-mediated clinical response.

Therefore, patients with tumor progression by RECIST imaging or laboratory parameters prior to week 18 but without rapid clinical deterioration or change in PS who do not require additional immediate therapy, may continue to be treated with ipilimumab and clinically observed following the assigned imaging schedule to allow detection of a subsequent tumor response. Patients will be taken off study at week 18 for disease progression if they have developed $\geq$5 new lesions that are at least 2cm in size from the week 10 scan. Tumor assessments will be made using RECIST or immune-related response criteria (irRC). In the case that the RECIST or irRC report is not complete by scheduled treatment date, the clinician may evaluate scans to assess whether a patient meets the above criteria to continue

treatment. If RECIST or irRC read later determines progression, the date of progression will be back-dated to the date of the scan.

6. DOSING DELAYS/DOSE MODIFICATIONS

6.1 Dose Modifications

6.1.1 Ipilimumab

Patients starting treatment at the 10 mg/kg dose that experience adverse events included on the list of exceptions to permanent discontinuation (**Section 6.4.2**) may have ipilimumab dose reduced to 3 mg/kg, following discussion with protocol chair and sponsor. No dose modifications will be allowed for patients starting treatment at 3 mg/kg. Ipilimumab dose delay parameters, skipping, and discontinuation rules are found in **Section 6.2, 6.3,** and **6.4**.

6.1.2 Allogeneic GM-CSF Transfected Pancreatic Tumor Vaccine (with or without cyclophosphamide)

No dose modifications will be allowed for the vaccine or the vaccine in combination with cyclophosphamide.

6.1.3 FOLFIRINOX

Decisions regarding FOLFIRINOX dose reductions and regimen modifications may be made by the patient's treating physician per standard of care practice.

6.2 Ipilimumab Dosing Delays

Dosing will be delayed for the following laboratory criteria:

- AST, ALT > 2.5 x ULN (AST, ALT >5 x ULN for patient with liver metastases)
- Total bilirubin >1.5 x ULN
- Hemoglobin < 8 g/dL
- ANC < 1000/uL
- Platelets < 80 x 10^3/uL

If, during the course of treatment an increase in LFT values are detected, ipilimumab should not be administered until approval by the protocol chair or sponsor. The subject should be evaluated and managed referring to the IB, management section, and algorithm in **Appendix C**, as clinically appropriate.

6.3 Ipilimumab Dose Skipping Rule

If there is a delay in dosing, doses can be made up so that a subject can still receive all 4 induction doses given that the doses are a minimum of 3 weeks apart and they have not experienced an adverse event necessitating discontinuation

All AEs that require holding drug treatment should be reviewed at the weekly conference call.

The investigator should contact the Protocol Chair or drug monitor to discuss any questions.

The following criteria will be used to determine dose holding, restarting doses, or discontinuing ipilimumab.

It is necessary to avoid study drug dosing and initiate appropriate evaluation and/or treatment for the following adverse events:

- Any ≥ grade 3 skin related adverse event regardless of causality.
- Any ≥ grade 2 non-skin related adverse event (including immune-mediated adverse reactions), except for easily correctly laboratory abnormalities that do not reflect underlying organ pathology.
- Any ≥ grade 3 laboratory abnormality.
- Any ≤ grade 2 cardiac toxicity. If both troponin and symptoms return to baseline and myocarditis is ruled out, treatment may be resumed.
- Any adverse event, laboratory abnormality or intercurrent illness that, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued dosing.
- It may be necessary to hold study drug to evaluate Grade 1 events that suggest ongoing or incipient autoimmune disease including GI toxicity, diarrhea, pancreatitis, hepatitis, pituitary insufficiency, early evidence of neurologic events, skin toxicity until diagnosis and progression are determined.

Ipilimumab may be restarted if/when the adverse event(s) resolve(s) or return(s) to < or = grade 1 within 2 weeks of the missed dose:

- If the adverse event has been determined not be related to ipilimumab or is not an autoimmune/inflammatory event.
- If the *adverse event has resolved to* **≤ grade 1** *,* ipilimumab dosing may be restarted. Please follow guidelines for specific events. Please note that re-initiating treatment may be associated with recurrence or exacerbation of autoimmune or inflammatory events. In some instances clinical resolution of events such as colitis may be associated with residual pathologic changes and should require evaluation of complete resolution prior to restarting therapy.
- Events which require intervention with immunosuppressant therapy, steroids, surgery, or hormone replacement generally require permanently stopping study treatment. Consult guidelines for exceptions and specific events.
- Autoimmune/inflammatory events are presumably related to the mechanisms of action of ipilimumab and potentially to a therapeutic effect. The incidence and severity of these events may be dose related, but once initiated, there is no evidence that lowered doses can be administered without continued autoimmune activity and there has so far been no demonstrable benefit to continuing ipilimumab after an autoimmune event during the initial

treatment. The significance and benefit of toxicity or continued treatment in the maintenance phase has not been determined.

6.4 Discontinuation of Ipilimumab

Patients that are required to stop treatment with ipilimumab due to toxicity per **Section 6.4.1** may stay on study and receive Vaccine in combination with low lose cyclophosphamide (200 mg/m^2) once the ipilimumab related toxicity(s) has resolved to a grade 1. Patients will resume treatment on the Cyclophosphamide + Vaccine calendar at the same point they discontinued treatment on the Vaccine + Ipilimumab calendar.

6.4.1 Permanent Discontinuation for Related Adverse Events

Permanently discontinue ipilimumab for any of the following:

- Any immune related grade 1-4 event (see exceptions below)
- Severe or life-threatening adverse reactions, including any of the following:
  - Colitis with abdominal pain, fever, ileus, or peritoneal signs; increase in stool frequency (7 or more over baseline), need for IV hydration for more than 24 hours, gastrointestinal hemorrhage, and gastrointestinal perforation
  - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >5 times the upper limit of normal or total bilirubin >3 times the upper limit of normal
  - Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations
  - Severe motor or sensory neuropathy, Guillain-Barré syndrome, or myasthenia gravis
  - Any ≥ grade 3 cardiac dysfunction, ≥ grade 2 myocarditis, or grade 2 cardiac dysfunction that does not return to baseline or reoccurs.
  - Severe immune-mediated reactions involving any organ system (*e.g.*, nephritis, pneumonitis, pancreatitis, non-infectious myocarditis)
  - Immune-mediated ocular disease that is unresponsive to topical immunosuppressive therapy
  - Any adverse event, laboratory abnormality or intercurrent illness which, in the judgment of the investigator, presents organ specific injury and/or a substantial clinical risk to the patient with continued dosing.

The following neurological adverse event requires permanent discontinuation of ipilimumab and defines unacceptable neurotoxicity:

- Any motor neurologic toxicity >/= grade 3 regardless of causality
- Any >/= grade 3 treatment related sensory neurologic toxicity

Please refer to **Appendix C** and the IB for specific treatment algorithms.

6.4.2 Exceptions to Permanent Discontinuation

- Potentially reversible inflammation (< grade 4), attributable to a local anti-tumor reaction and a potential therapeutic response. This includes inflammatory reactions at sites of tumor resections or in draining lymph nodes, or at sites suspicious for, but not diagnostic of metastasis.
- Hospitalization for ≤ grade 3 adverse events where the primary reason for hospitalization is to expedite the clinical work-up.
- Patients with the following conditions where in the investigator's opinion continuing study drug administration is justified based on the potential for continued clinical benefit:
  - ≤ Grade 3 skin rash treated with steroids for less than 4 weeks
  - ≤ Grade 2 Ocular toxicity that has completely responded to topical therapy within 4 weeks
  - Endocrinopathies where clinical symptoms are controlled with appropriate hormone replacement therapy. **Note:** Ipilimumab may not be restarted while the patient is being treated with systemic corticosteroids except for patients on stable doses of hormone replacement therapy such as hydrocortisone.
  - Asymptomatic lipase elevations of any grade may be retreated once resolved to patient's baseline grade.

6.4.3 Immune-Related Adverse Events (irAEs) Reactions and Immune-mediated Adverse Reactions: Definition, Monitoring, and Treatment

For the purposes of this study, an immune-related adverse reaction is defined as an adverse reaction of unknown etiology associated with drug exposure and consistent with an immune phenomenon. Efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an event an irAEs. Serologic, immunologic, and histologic (biopsy) data should be used to support the diagnosis of an immune-related toxicity. Suspected immune-related adverse reactions must be documented on an AE or SAE form. Another term for an irAE is an immune-mediate adverse reaction, as it is termed in the Ipilimumab US Prescribing Information. Both terms may be used in this protocol document.

Patients should be informed of and carefully monitored for evidence of clinically significant systemic immune-mediated adverse reactions (e.g., systemic lupus erythematosus-like diseases) or organ-specific immune-mediated adverse reaction(e.g., rash, colitis, uveitis, hepatitis or thyroid disease). If an immune-mediated adverse reaction is noted, appropriate work-up (including biopsy if possible) should be performed, and steroid therapy may be considered if clinically necessary.

It is unknown if systemic corticosteroid therapy has an attenuating effect on ipilimumab activity. However, clinical anti-tumor responses have been maintained in patients treated with corticosteroids and discontinued from ipilimumab. If utilized, corticosteroid therapy

should be individualized for each patient. Prior experience suggests that colitis manifested as ≥ grade 3 diarrhea requires corticosteroid treatment.

Recommended guidelines for specific immune-mediated adverse reactions are included in section 6.4.4 below, in **Appendix C**, and the package insert. These recommendations should be utilized as clinically appropriate for the treatment of individual patients. Please contact the PI or drug monitor for any questions.

6.4.4 Other Guidance

The following guidance is provided for the management of ipilimumab treatment related events. These recommendations, treatment algorithms in **Appendix C**, and further information in the IB, should be considered in the context of appropriate medical treatment for each patient.

6.4.4.1 Treatment of Infusion Reactions Associated with Ipilimumab

Since ipilimumab contains only human protein sequences, it is less likely that any allergic reaction will be seen in patients. However, it is possible that infusion of ipilimumab will induce a cytokine release syndrome that could be evidenced by fever, chills, rigors, rash, pruritus, hypotension, hypertension, bronchospasm, or other symptoms. No prophylactic pre-medication should be given unless indicated by previous experience in an individual patient. Reactions should be treated based upon the following recommendations.

- For mild symptoms (*e.g.*, localized cutaneous reactions such as mild pruritus, flushing, rash):
  - Decrease the rate of infusion until recovery from symptoms, remain at bedside and monitor patient.
  - Complete the ipilimumab infusion at the initial planned rate.
  - Diphenhydramine 50 mg IV may be administered at the discretion of the treating physician and patients may receive additional doses with close monitoring.
  - Premedication with diphenhydramine may be given at the discretion of the investigator for subsequent doses of ipilimumab.
- For moderate symptoms (any symptom not listed above [mild symptoms] or below [severe symptoms] such as generalized pruritus, flushing, rash, dyspnea, hypotension with systolic BP >80 mmHg):
  - Interrupt ipilimumab.
  - Administer diphenhydramine 50 mg IV.
  - Monitor patient closely until resolution of symptoms.
  - Corticosteroids may abrogate any beneficial immunologic effect, but may be administered at the discretion of the treating physician.
  - Resume ipilimumab infusion after recovery of symptoms.

  - At the discretion of the treating physician, ipilimumab infusion maybe resumed at *one half the initial infusion rate, then increased incrementally to the initial infusion rate.*
  - If symptoms develop after resumption of the infusion, the infusion should be discontinued and no additional ipilimumab should be administered that day.
  - The next dose of ipilimumab will be administered at its next scheduled time and may be given with pre-medication (diphenhydramine and acetaminophen) and careful monitoring, following the same treatment guidelines outlined above.
  - At the discretion of the treating physician additional oral or IV antihistamine may be administered prior to dosing with ipilimumab.
- For severe symptoms (e.g., any reaction such as bronchospasm, generalized urticaria, systolic blood pressure <80 mm Hg, or angioedema):
  - Immediately discontinue infusion of ipilimumab, and disconnect infusion tubing from the subject.
  - Consider bronchodilators, epinephrine 1 mg IV or subcutaneously, and/or diphenhydramine 50 mg IV, with solumedrol 100 mg IV, as needed.
  - Patients should be monitored until the investigator is comfortable that the symptoms will not recur.
  - No further ipilimumab will be administered.
- In case of late-occurring hypersensitivity symptoms (e.g., appearance within one week after treatment of a localized or generalized pruritus), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).

6.4.4.2 Treatment of Ipilimumab-Related Isolated Drug Fever

In the event of isolated drug fever, the investigator must use clinical judgment to determine if the fever is related to the ipilimumab or to an infectious etiology. If a patient experiences isolated drug fever, for the next dose, pre-treatment with acetaminophen or non-steroidal anti-inflammatory agent (investigator discretion) should be instituted and a repeated antipyretic dose at 6 and 12 hours after ipilimumab infusion, should be administered. The infusion rate will remain unchanged for future doses. If a patient experiences recurrent isolated drug fever following premedication and post dosing with an appropriate antipyretic, the infusion rate for subsequent dosing should be decreased to 50% of the previous rate. If fever recurs following infusion rate change, the investigator should assess the patient's level of discomfort with the event and use clinical judgment to determine if the patient should receive further ipilimumab.

6.4.4.3 Monitoring and Management of Immune-mediated Adverse Reactions

<u>Immune-mediated Enterocolitis</u>
The clinical presentation of GI immune-related AEs included diarrhea, increase in the frequency of bowel movements, abdominal pain, or hematochezia, with or without fever. However inflammation may occur in any part of the GI tract including esophagitis and gastritis. Fatalities due to GI perforation have been reported in clinical

trials of ipilimumab. Patients should be carefully monitored for GI symptoms that may be indicative of immune-related colitis, diarrhea, or GI perforation. Diarrhea or colitis occurring after initiation of ipilimumab therapy should be evaluated to exclude infectious or alternate etiologies. In clinical trials, immune-related colitis was associated with evidence of mucosal inflammation, with or without ulcerations, and lymphocytic infiltration.

Monitor patients for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, mucus or blood in stool, with or without fever) and bowel perforation (such as peritoneal signs and ileus). In symptomatic patients, rule out infectious etiologies and consider endoscopic evaluation to establish etiology and for persistent or severe symptoms. *C. difficile* toxin has been detected in several patients with colitis and may be an independent entity or may co-exist with ipilimumab induced inflammatory colitis.

Withhold ipilimumab dosing for any patients with enterocolitis pending evaluation; administer anti-diarrheal treatment and, if persistent evaluate with colonoscopy and initiate systemic corticosteroids at a dose of 0.5 mg/kg/day prednisone or equivalent.

Permanently discontinue ipilimumab in patients with severe enterocolitis and initiate systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. Upon improvement to grade 1 or less, initiate corticosteroid taper and continue to taper over at least one month. In clinical trials, rapid corticosteroid tapering has resulted in recurrence or worsening symptoms of enterocolitis in some patients.

Patients have been treated with anti-TNF agents for persistent colitis not responding to steroids.

Please note autoimmune pancreatitis may cause abdominal pain and should be included in all evaluations. Enteritis may occur occasionally with other autoimmune events including hepatitis, pancreatitis, and endocrine insufficiency, which should be evaluated as clinically indicated.

<u>Immune-mediated Hepatitis and Pancreatitis</u>
Hepatic immune-related AEs were mostly clinically silent and manifested as transaminase or bilirubin laboratory abnormalities. Fatal hepatic failure has been reported in clinical trials of ipilimumab. **Serum transaminase and bilirubin and lipase levels must be evaluated before each dose of ipilimumab as early laboratory changes may be indicative of emerging immune-related hepatitis/ pancreatitis and elevations in liver function tests (LFTs) may develop in the absence of clinical symptoms.** Increase in LFT or total bilirubin should be evaluated to exclude other causes of hepatic injury, including infections, disease progression, or other medications, and monitored until resolution. Liver biopsies from patients who had immune-related hepatotoxicity showed evidence of acute inflammation (neutrophils, lymphocytes, and macrophages).

Monitor liver function tests (hepatic transaminase and bilirubin levels, lipase) and assess patients for signs and symptoms of hepatotoxicity/ pancreatitis before each dose of ipilimumab. In patients with hepatotoxicity, rule out infectious or malignant causes and increase frequency of liver function test monitoring until resolution. Withhold ipilimumab in patients with grade 2 hepatotoxicity.

Permanently discontinue ipilimumab in patients with grade 3–5 hepatotoxicity/pancreatitis and administer systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When liver function tests show sustained improvement or return to baseline, initiate corticosteroid tapering and continue to taper over 1 month. Across the clinical development program for ipilimumab, mycophenolate treatment has been administered in patients who have persistent severe hepatitis despite high-dose corticosteroids.

Immune-mediated Dermatitis

Skin immune-related AEs presented mostly frequently as a rash and/or pruritus. Some subjects reported vitiligo associated with ipilimumab administration. Fatal toxic epidermal necrolysis has been reported in clinical trials of ipilimumab.

Monitor patients for signs and symptoms of dermatitis such as rash and pruritus. Unless an alternate etiology has been identified, signs or symptoms of dermatitis should be considered immune-mediated.

Permanently discontinue ipilimumab in patients with Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations. Administer systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When dermatitis is controlled, corticosteroid tapering should occur over a period of at least 1 month. Withhold ipilimumab dosing in patients with moderate to severe signs and symptoms.

For mild to moderate dermatitis, such as grade 2 localized rash and pruritus, treat symptomatically. For persistent grade 2, grade 3, or greater, topical steroids may be administered. Administer topical or systemic corticosteroids as indicated if there is no improvement of symptoms within 1 week.

Immune-related Neurological Events

Fatal Guillain-Barré syndrome has been reported in clinical trials of ipilimumab. Patients may present with muscle weakness and myasthenia gravis, cranial nerve palsy (n VII Bell's palsy), and aseptic meninigits, encephalopathy. Unexplained motor neuropathy, muscle weakness, or sensory neuropathy lasting more than 4 days should be evaluated and non-inflammatory causes such as disease progression, infections, metabolic syndromes, nerve entrapment, and medications should be excluded as causes.

Withhold ipilimumab dosing in patients with any evidence of neuropathy pending evaluation.

Monitor for symptoms of motor or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, or paresthesia. Permanently discontinue ipilimumab in patients with severe neuropathy (interfering with daily activities) such as Guillain-Barré-like syndromes. Institute medical intervention as appropriate for management of neuropathy and other neurologic events. Consider initiation of systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent for severe neuropathies.

Immune-mediated Endocrinopathies

Ipilimumab can cause inflammation of endocrine organs including thyroid (Hashimoto's thryroiditis with positive antibodies) and adrenal glands, hypophysitis, hypopituitarism, and resulting thyroid and adrenal insufficiency, low ADH, prolactin, FSH, LH. Hyperthyroid with Graves' disease and positive antibody has been reported. Patients may present with subtle and nonspecific symptoms. The most common clinical presentation includes headache and fatigue. Symptoms may also include visual field defects, behavioral changes, and electrolyte disturbances including hyponatremia and hypotension. Adrenal crisis as a cause of the patient's symptoms should be excluded. Based on the available data with known outcome, most of the subjects symptomatically improved with hormone replacement therapy. Long-term hormone replacement therapy with HC and synthroid will typically be required for subjects developing hypophysitis/hypopituitarism after treatment with ipilimumab. Some patients have regained partial function following steroid treatment.

Monitor patients for clinical signs and symptoms of hypophysitis, adrenal insufficiency (including adrenal crisis), and hyper- or hypothyroidism. Headache is often the first symptoms of hypophysitis. Patients may present with fatigue, headache, mental status changes, loss of libido, abdominal pain, unusual bowel habits, and hypotension, or nonspecific symptoms which may resemble other causes such as brain metastasis or underlying disease. Unless an alternate etiology has been identified, signs or symptoms of endocrinopathies should be considered immune-mediated and drug withheld pending evaluation. Patients may demonstrate both central (hypophysitis) and peripheral adrenal and thyroid insufficiency. Evaluation of hypophysitis should include pituitary MRI.

Endocrine evaluation, including TSH, should be performed at baseline prior to initial treatment. Monitor thyroid function tests and clinical chemistries at the start of treatment and hold blood for possible evaluation should clinical events require determining baseline function and anti-thyroid antibodies. A plan for evaluating endocrine function at each visit either by history or monitoring TSH should be included in the protocol with further evaluation as clinically indicated. Endocrine evaluation, including TSH, should be performed at baseline prior to treatment, and the protocol must include a plan for continued monitoring of endocrine and pituitary function. The package insert for ipilimumab includes a recommendation for monitoring TSH prior to each infusion; as an early indication for pituitary dysfunction and hypophysitis, clinical monitoring of symptoms may be equally or more sensitive as an initial presentation.

Clinical monitoring is required for all protocols as above, and should include any requirements per protocol for laboratory evaluation, both periodically or as clinically indicated, consistent with good medical practice. In a limited number of patients, hypophysitis was diagnosed by imaging studies through enlargement of the pituitary gland.

Withhold ipilimumab dosing in patients symptomatic for hypophysitis. Initiate systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent, and initiate appropriate hormone replacement therapy.

Immune-mediated Cardiotoxicity

Evaluation of cardiac function, including EKG and echocardiogram (ECHO), will be done for any patients with a history of CHF or at risk because of underlying cardiovascular disease or exposure to cardiotoxic drugs as clinically indicated. For patients who develop evidence of CHF, MI, cardiomyopathy, or myositis while on study, cardiac evaluation including lab tests and cardiology consultations will be done as clinically indicated including EKG, CPK, troponin, and ECHO. Treatment with steroids should be started as clinically indicated. Drug will be permanently discontinued for grade 3 or 4 cardiac dysfunction and grade 2 events that do not recover to baseline or that reoccur. See table below for additional guidelines for management of cardiac toxicities.

Cardiac Toxicities *	**Management/Next Dose for Ipilimumab Cardiac Toxicities**
≤ Grade 1	Hold dose pending evaluation and observation.** Evaluate for signs and symptoms of CHF, ischemia, arrhythmia or myositis. Obtain history EKG, CK (for concomitant myositis), CK-MB. Repeat troponin, CK and EKG 2-3 days. If troponin and labs normalize may resume therapy. If labs worsen or symptoms develop then treat as below. Hold pending evaluation.
Grade ≥2 with suspected myocarditis	Hold dose.** Admit to hospital. Cardiology consult. Rule out MI and other causes of cardiac disease. Cardiac Monitoring. Cardiac Echo. Consider cardiac MRI and cardiac biopsy. Initiate high dose methylprednisolone. If no improvement within 24 hours, add either infliximab, ATG or tacrolimus. Consult algorithm for more details. Resume therapy if there is a return to baseline and myocarditis is excluded or considered unlikely.
Grade ≥2 with confirmed myocarditis	Off protocol therapy. Admit to CCU (consider transfer to nearest Cardiac Transplant Unit). Treat as above. Consider high dose methylprednisolone. Add ATG or tacrolimus if no improvement. Off treatment.
** Including CHF, LV systolic dysfunction, Myocarditis, CPK, and troponin* *** Patients with evidence of myositis without myocarditis may be treated according as "other event"*	

Note: The optimal treatment regimen for immune mediated myocarditis has not been established. Since this toxicity has caused patient deaths, an aggressive approach is recommended.

Other Immune-mediated Adverse Reactions, Including Ocular Manifestations
Ocular inflammation, manifested as grade 2 or grade 3 episcleritis or uveitis, was associated with concomitant diarrhea in a few subjects (<1%) and occasionally occurred in the absence of clinically apparent GI symptoms. Other presumed immune-related AEs reported include, but were not limited to, arthritis/arthralgias, pneumonitis, pancreatitis, autoimmune (aseptic) meningitis, autoimmune nephritis, pure red cell aplasia, noninfective myocarditis, polymyositis, and myasthenia gravis, of which were individually reported for <1% of subjects.

The following clinically significant immune-mediated adverse reactions were seen in less than 1% of ipilimumab-treated patients in Study 1: nephritis, pneumonitis, pulmonary granuloma resembling sarcoidosis, meningitis, pericarditis, uveitis, iritis, ITP, neutropenia and hemolytic anemia.

Across the clinical development program for ipilimumab, the following likely immune-mediated adverse reactions were also reported with less than 1% incidence: myocarditis, angiopathy, temporal arteritis, vasculitis, polymyalgia rheumatica, conjunctivitis, blepharitis, episcleritis, scleritis, leukocytoclasticvasculitis, erythema multiforme, psoriasis, pancreatitis, arthritis, and autoimmune thyroiditis.

Permanently discontinue ipilimumab for clinically significant or severe immune-mediated adverse reactions. Initiate systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent for severe immune-mediated adverse reactions.

Administer corticosteroid eye drops to patients who develop uveitis, iritis, or episcleritis. Permanently discontinue ipilimumab for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy.

Overall, immune-related AEs commonly started within 3 to 10 weeks from first dose, were successfully managed in most instances by omitting doses, discontinuing dosing, and/or through administering symptomatic or immunosuppressive therapy, including corticosteroids, as mentioned above. Immune-related AEs generally resolved within days to weeks in the majority of subjects.

6.4.5 Precautions

Combination therapy may result in unexpected toxicity especially in novel combinations with other immune modifying agents. A striking example involving fatal pancreatitis in macaques is presented in Vaccari*, et al.* 2012.

Please note that while unproven, there is a suggestion that autoimmune events, including hepatitis, may occur more frequently at sites of metastases or prior injury.

Caution is advised when considering treatment with high-dose IL-2 in patients who have previously been administered ipilimumab, particularly in patients who experienced ipilimumab-related diarrhea/colitis. Colonoscopy or sigmoidoscopy with biopsy may be advisable prior to IL-2 administration once the patient is no longer receiving ipilimumab. The management guidelines for general inflammatory AEs and ipilimumab-related GI toxicities, hepatotoxicity, endocrinopathy, and neuropathy (Investigator Brochure, 2011) are provided in **Appendix C**.

Patients who have received ipilimumab may potentially develop autoimmune disease with subsequent therapy including the appearance of colitis, hypophysitis or adrenal insufficiency.

6.4.6 Study Procedures by Visit and Treatment Cycle

Note that results of all safety laboratory tests (that is, all chemistry and all hematology results) must be obtained and reviewed before ipilimumab administration, as applicable. All laboratory results must be within the established range before ipilimumab is administered. All induction period laboratory samples must be collected within a window of up to 4 days before administration of ipilimumab. Laboratory evaluations using a local laboratory must be performed and the result examined by the investigator before administration of each dose of ipilimumab.

7. ADVERSE EVENTS: REPORTING REQUIREMENTS

This study will use the descriptions and grading scales found in the revised National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 for adverse event reporting that can be found at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected, recorded, and followed as appropriate.

All adverse events experienced by subjects in Arm A will be collected and reported from the first dose of the investigational agent, throughout the study, and will only be followed for 70 days unless related to the investigational agent. AEs will not be collected for patients in Arm B, as they will continue with standard of care treatment.

Subjects who have an ongoing adverse event related to the study procedures and/or medication(s) may continue to be periodically contacted by a member of the study staff until the event is resolved or determined to be irreversible by the investigator.

Laboratory abnormalities: Laboratory abnormalities present at the screening visit will be recorded as pre-treatment signs and symptoms. After study treatment administration, 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.

7.1 Definitions

7.1.1 Adverse Event (AE)

Adverse event is defined as any undesirable sign, symptom or medical condition occurring after starting the study drug (or therapy) even if the event is not considered to be related to the study. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). Medical conditions/diseases present before starting the study treatment are only considered adverse events if they worsen after starting the study treatment (any procedures specified in the protocol). Adverse events occurring before starting the study treatment but after signing the informed consent form will be not recorded. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy.

7.1.2 Serious Adverse Event (SAE)

A serious adverse event is an undesirable sign, symptom or medical condition which:
• Results in death
• Is life threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
• Requires inpatient hospitalization or causes prolongation of existing hospitalization (see note below for exceptions) for ≥ 24 hours
• Results in persistent or significant disability/incapacity
• Is a congenital anomaly/birth defect (note: reports of congenital anomalies/birth defects must also be reported on the Pregnancy Supplemental Form)
• Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)

Events **not** considered to be serious adverse events are hospitalizations for the:
• Admissions as per protocol for a planned medical/surgical procedure

• Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
• Medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases
• Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).

7.2 Relationship

Definite – The AE *is clearly related* to the study treatment.
Probable – The AE *is likely related* to the study treatment.
Possible – The AE *may be related* to the study treatment.
Unlikely – The AE *is doubtfully related* to the study treatment.
Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expectedness

Unexpected adverse event: An adverse event, which varies in nature, intensity or frequency from information on the investigational drug/agent provided in the Investigator's Brochure, package insert or safety reports. Any adverse event that is not included in the informed consent is considered "unexpected".

Expected (known) adverse event: An adverse event, which has been reported in the Investigator's Brochure. An adverse event is considered "expected", only if it is included in the informed consent document as a risk.

7.4 Handling of Expedited Safety Reports

In accordance with local regulations, CTEP (or Sponsor) will notify investigators of all SAEs that are unexpected (ie, not previously described in the Investigator Brochure), and definitely, probably, or possibly related to Ipilimumab (or the Pancreatic Tumor Vaccine). This notification will be in the form of an expedited safety report (ESR) that is to be faxed to Dr. Dung Le and the study coordinator within 48 hours.

Upon receiving such notices, the investigator must review and retain the notice with the Investigator's Brochure and where required by local regulations, the investigator will submit the ESR to the appropriate IRB/IBC. The investigator and IRB/IBC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IBC procedures for reporting any other safety information. Where required, submission of ESRs by the investigator to Health Authorities should be handled according to local regulations. Dr. Dung Le will also be responsible for notifying all other investigators participating in the study of these adverse events.

7.5 Reporting

7.5.1 General

All adverse events (both expected and unexpected) will be captured on the appropriate study-specific case report forms (CRFs). In addition, all serious adverse events, regardless of causality to study drug and/or administration device, will be reported promptly to Dr. Elizabeth Jaffee [redacted] Dr. Dung Le [redacted] and the coordinating center [redacted] within 24 hours of recognition of the adverse event using the form found in **Appendix D**. Each site will be responsible for submitting its own SAEs to CTEP-AERS..

7.5.2 Institutional Review Board (IRB) and Institutional Biosafety Committee (IBC)

Participating sites will be responsible for reporting to their institutional IRB and IBC. All serious adverse events will be reported to the Institutional Review Board (IRB) and IBC per institutional standards within 3 days of recognition of the adverse event if the event is related and expected, related and unexpected, or related and fatal or life-threatening due to administration of the investigational product(s). If the serious adverse event is unrelated to administration of the investigational agents, then it will be reported to the IRB and IBC within 15 days of recognition of the serious adverse event. Follow-up information will be submitted to the IRB and IBC as soon as relevant information is available.

7.5.3 Food and Drug Administration (FDA)

This is a multi-institutional trial. All reporting to the FDA will be completed by the Sponsor.

7.5.3.1 Expedited IND Safety Reports:

7 Calendar-Day Telephone or Fax Report:
The Sponsor is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the investigational agent. Such reports are to be telephoned or faxed (301-827-9796) to the FDA within 7 calendar days of first learning of the event. Follow-up information will be submitted to the FDA as soon as relevant information is available.

15 Calendar-Day Written Report:
The Sponsor is required to notify the FDA of any serious adverse event that is unexpected and possibly related to the investigational agent in a written IND Safety Report.

Written IND Safety Reports should include an Analysis of Similar Events in

accordance with regulation 21 CFR § 312.32. All safety reports previously filed with the IND concerning similar events should be analyzed. The new report should contain comments on the significance of the new event in light of the previous, similar reports.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA within 15 calendar days of first learning of the event. Follow-up information will be submitted to the FDA as soon as relevant information is available.

The coordinating center will also be responsible for submitting a copy of IND safety reports to CTEP [redacted]

7.5.3.2 IND Annual Reports

In accordance with the regulation 21 CFR § 312.33, the Sponsor shall within 60 days of the anniversary date that the IND went into effect submit a brief report of the adverse events and progress of the investigation. Please refer to Code of Federal Regulations, 21 CFR § 312.33 for a list of the elements required for the annual report. All IND annual reports will be submitted to the FDA by the Sponsor. The coordinating center will be responsible for submitting a copy of the annual report to CTEP.

7.5.4 CTEP-AERS

Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov).

See **Appendix E** for the CAEPR and SPEER list to determine if expedited reporting is required. An additional list of risk profile list for Ipilimumab is also provided in **Appendix F** as to be easily identified by investigators.

AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.

The sponsor ([redacted] principal investigator [redacted] and study coordinating center representative [redacted] should be included in the list of recipients (or cc list) for any expedited reports sent through CTEP-AERs.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

ALL SERIOUS adverse events that meet the criteria in **Section 7.1.2** MUST be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4&5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour
5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
<tr><td colspan="5">NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.</td></tr>
</table>

Serious adverse events that occur more than 70 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

7.5.5 Recombinant DNA Advisory Committee (RAC)

RAC reporting for all sites will be completed by the coordinating center. Unexpected adverse events believed to be definitely, probably, or possibly related to the investigational product (s) will be reported to RAC by email if fatal or life-threatening within 7 calendar days or by written report if related and unexpected to the investigational product(s) within 15 calendar days. Serious adverse events that are

unrelated or related and expected with the investigational product (s) will be reported to RAC in the Annual Report. Upon receipt of the report of the adverse event by RAC, follow-up information will be provided to RAC within 15 days.

7.6 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm. CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event.

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocyticleukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

7.7 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine reporting via CDUS unless otherwise specified.

8. PHARMACEUTICALINFORMATION

8.1 Ipilimumab

[redacted]

[redacted]

[redacted]

8.2 Allogeneic GM-CSF Transfected Pancreatic Tumor Vaccine

[redacted]

[redacted]

8.3 FOLFIRINOX

8.3.1 5- Fluorouracil

Commercial Supply - Please refer to the package insert for further information on 5-Fluorouracil.

Product description: Fluorouracil, an antineoplastic antimetabolite, is a colorless to yellow aqueous sterile nonpyrogenic injectable solution. Each mL contains: 50 mg fluorouracil; pH is adjusted to approximately 9.2 with sodium hydroxide.

Solution preparation: Stable for prolonged periods of time at room temperature if protected from light. Note manufacturer's expiration date. Inspect for precipitate; if apparent, agitate vial vigorously or gently heat to not greater than 140°F in a water bath. Do not allow to freeze. Dilution is not required.

Route of administration: 5-Fluorouracil is administered by intravenous injection or orally if subject is receiving capecitabine therapy.

8.3.2 Irinotecan

Commercial Supply - Please refer to the package insert for further information on irinotecan.

Product description: Irinotecan, an antineoplastic agent of the topoisomerase I inhibitor class, is a sterile, pale yellow, clear, aqueous solution. It is available in two single-dose sizes in brown glass vials: 2 mL-fill vials contain 40 mg irinotecan hydrochloride and 5 mL-fill vials contain 100 mg irinotecan hydrochloride. Each milliliter of solution contains 20 mg of irinotecan hydrochloride (on the basis of the trihydrate salt), 45 mg of sorbitol, NF, and 0.9 mg of lactic acid, USP. The pH of the solution has been adjusted to 3.5 (range, 3.0 to 3.8) with sodium hydroxide or hydrochloric acid.

Solution preparation: Store at controlled room temperature 15° to 30°C (59° to 86°F). Protect from light. It is recommended that the vial should remain in the carton until the time of use. Dilute irinotecan with 5% Dextrose Injection, USP (D5W), or 0.9% Sodium Chloride Injection, USP, prior to intravenous infusion. The preferred diluent is 5% Dextrose Injection, USP.

Route of administration: Irinotecan is administered by intravenous injection.

8.3.3 Leucovorin

Commercial Supply - Please refer to the package insert for further information on leucovorin.

Product description: Leucovorin, a derivative of folic acid, is a lyophilized powder. In each dosage form, one milligram of leucovorin calcium contains 0.002 mmol of leucovorin and 0.002 mmol of calcium. The inactive ingredient is sodium chloride 180 mg/vial for the 200 mg and 450 mg/vial for the 500mg. Sodium hydroxide and/or hydrochloric acid may be added for pH adjustment. pH adjusted to approximately 7.8.

Solution preparation: All dosage forms are stored at room temperature. Protect from light. Reconstitute the lyophilized vial products with Bacteriostatic Water for Injection, USP (benzyl alcohol preserved), or Sterile Water for Injection, USP. When reconstituted with Bacteriostatic Water for Injection, USP, the resulting solution must be used within 7 days. If the product is reconstituted with Sterile Water for Injection, USP, use immediately and discard any unused portion.

Route of administration: Leucovorin is administered by intravenous injection.

8.3.4 Oxaliplatin

Commercial Supply - Please refer to the package insert for further information on oxaliplatin.

Product description: Oxaliplatin, an antineoplastic agent, is a sterile, preservative-free lyophilized powder for reconstitution. Lactose monohydrate is present as an inactive ingredient at 450 mg and 900 mg in the 50 mg and 100 mg dosage strengths, respectively.

Solution preparation: Refer to package insert for complete preparation and dispensing instructions. Store intact vials in original outer carton at room temperature and; do not freeze. According to the manufacturer, solutions diluted for infusion are stable up to 6 hours at room temperature or up to 24 hours under refrigeration. The lyophilized powder is reconstituted with water for injection (USP) or 5% dextrose injection (USP). Do not prepare using a chloride-containing solution (e.g., NaCl). The reconstituted solution must be further diluted in an infusion solution of 250-500 mL of 5% Dextrose Injection, USP. Infusion solutions do not require protection from light.

Route of administration: Oxaliplatin is administered by intravenous injection.

8.4 Cyclophosphamide (Cytoxan)

Mode of Action: Cyclophosphamide is a synthetic antineoplastic drug chemically related to the nitrogen mustards. Cyclophosphamide is biotransformed principally in the liver to active alkylating metabolites by a mixed function microsomal oxidase system. These metabolites interfere with the growth of susceptible rapidly proliferating malignant cells. The mechanism of action is thought to involve cross-linking of tumor cell DNA.

Product description: CYTOXAN® (cyclophosphamide for injection, USP) is a sterile white powder containing cyclophosphamide monohydrate and is supplied in vials for single-dose use.

Storage and Dispensing: Cyclophosphamide (prepared for either direct injection or infusion) is chemically and physically stable for 24 hours at room temperature or for six days in the refrigerator; it does not contain any antimicrobial preservative and thus care must be taken to assure the sterility of prepared solutions.

Preparation: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Add the diluent to the vial and shake it vigorously to dissolve. If the powder fails to dissolve immediately and completely, it is advisable to allow the vial to stand for a few minutes. Use the quantity of diluent shown below to constitute the product:

Dosage Strength	CYTOXAN Contains Cyclophosphamide Monohydrate	Quantity of Diluent
500 mg	534.5 mg	25 mL
1 g	1069.0 mg	50 mL
2 g	2138.0 mg	100 mL

CYTOXAN (cyclophosphamide) may be prepared for parenteral use by infusion using any of the following methods:

1. CYTOXAN constituted with 0.9% sterile sodium chloride may be infused without further dilution.
2. CYTOXAN constituted with 0.9% sterile sodium chloride may be infused following further dilution in the following:
    Dextrose Injection, USP (5% dextrose)
    Dextrose and Sodium Chloride Injection, USP (5% dextrose and 0.9% sterile sodium chloride)
    5% Dextrose and Ringer's Injection
    Lactated Ringer's Injection, USP
    Sodium Chloride Injection, USP (0.45% sterile sodium chloride)
    Sodium Lactate Injection, USP (1/6 molar sodium lactate)

Route of administration: Cyclophosphamide is administered by intravenous injection over 30 minutes.

Patient Care Implications:
During treatment, the patient's hematologic profile (particularly neutrophils and platelets) should be monitored regularly to determine the degree of hematopoietic suppression.

The rate of metabolism and the leukopenic activity of cyclophosphamide reportedly are increased by chronic administration of high doses of phenobarbital. The physician should be alert for possible combined drug actions, desirable or undesirable, involving cyclophosphamide even though cyclophosphamide has been used successfully concurrently with other drugs, including other cytotoxic drugs. Cyclophosphamide treatment, which causes a marked and persistent inhibition of cholinesterase activity, potentiates the effect of succinylcholine chloride. If a patient has been treated with cyclophosphamide within 10 days of general anesthesia, the anesthesiologist should be alerted.

Cyclophosphamide may interfere with normal wound healing.

Availability: Cyclophosphamide is commercially available.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Biomarker Studies

N/A

9.2 Laboratory Correlative Studies

Mesothelin-specific T cell responses. Post-vaccination induction of mesothelin-specific T cell responses will be measured and correlated with OS. PBL will be collected at baseline and with each treatment in the vaccine arm. In the chemotherapy arm, PBL will be collected at baseline and at 6 weeks. PBL are isolated and stored frozen until use in assays as previously described (Thomas, *et al*, 2004). $CD8^+$ T cells will be enriched by negative selection using Dynal

Dynabeads. HLA-typing will be performed by the Johns Hopkins Immunodiagnostics CORE facility. We will use the same methods we have reported on to assay mesothelin-specific T cell responses in patients with HLA-A1, A2, A3, and A24 alleles. We also previously reported our prediction and validation methods for new peptides (Laheru, *et al*, 2008). Quantification of mesothelin-specific T cell responses and changes in T cell repertoire will be performed using IFNγ ELISPOT assays. $CD8^+$ T cells specific to each MHC class I restricted mesothelin peptide will be individually quantified in each PBL sample. T2 cells will be used to present epitopes. We have genetically modified T2 cells to express A1, A3, and A24. The cells naturally express HLA-A2. The CEF (CMV, EBV, influenza) pool will be used as positive control peptides and HIV, renal cell, or melanoma epitopes will be used as negative controls. Similar to our other reported studies, a $\geq$ 2-fold induction of mesothelin-specific T cell responses will be considered positive. The size of the mesothelin-specific T cell repertoire is the total number or percentage of epitopes for which an induction is measured. Evaluation of avidity changes in the mesothelin-specific T cell repertoire will be performed using dilutional tetramer staining. Tetramers are manufactured by Beckman Coulter and currently available for each of the 6 HLA-A0201-binding epitopes and under development for the 7 HLA-A0101 epitopes. Based on our published studies, tetramer dilutions ranging from 1:10 to 1:500 will be tested. The relative avidity for each mesothelin epitope is defined by the dilution at which tetramer staining is lost using flow cytometry. The distribution of avidities for each epitope will be used to define cutoffs for distinguishing high from low avidity T cell responses. The induction of a high avidity T cell repertoire will be correlated with OS. Tetramer analyses will also be performed to assess for the presence of high avidity T cells in the tumor itself using post-treatment biopsy samples.

Telomere length of lymphocytes as predictors of response. Telomere length will be measured on peripheral blood mononuclear cells using a highly robust method currently in clinical use. The method relies on a combined flow cytometry and fluorescence in situ hybridization which used diagnostically in genetic syndromes associated with telomere dysfunction (Armanios, *et al*, 2007; Alder, *et al*, 2008; Armanios, *et al*, 2012). The CLIA-approved assay will be performed by the Armanios group within the Johns Hopkins Clinical Pathology Laboratory.

Galectin-3 antibody responses as a correlative of response. We have developed an ELISA to detect vaccine induced galectin-3 antibody responses. EIA/RIA plates (Corning) are coated with purified recombinant proteins at 5 μg/ml at 4°C overnight. The protein-coated plates are incubated with ELISA Blocker Blocking Buffer (Pierce Biotech) for 1 h at room temperature, and then with 30 μl/well of serial dilutions (1:100, 1:200, 1:400, and 1:800) of sera (duplicates for each dilution) for 2 h at room temperature and with 30 μl/well of 1:200,000 dilution of goat antihuman IgG (γ-chain specific) peroxidase conjugate (Sigma, A8419) for 1 h at room temperature. The wells are washed with TBS-T between incubations. The plates are color developed with 3,3'5,5'-tetramethylbenzidine liquid substrate (Sigma, T0440) and incubated in the dark for 20 min at room temperature. The color development is stopped with 1 N sulfuric acid. Absorbance at 450 nm (with a reference wavelength of 570 nm) is measured on a PowerWave 340 microplate reader (BioTek). A galectin-3 antibody control curve is performed in advance with a positive serum sample (based on Western blot analysis) to have an OD450 of about 1.000 at serum dilution of 1:100. For each experiment, a control ELISA will be performed simultaneously with a second set of plates coated with only coating buffer for background subtraction. Antibody titer in a serum sample will be reported as OD450 at serum dilution of 1:400 after background subtraction. To ensure within run

reproducibility of the assay, duplicates will be done in different plates. For between-run reproducibility of the assays done on different days, a set of calibrating serum samples from 6 healthy donors with different antibody titers to a given protein will be run with each assay.

Proteomic approaches to identify potential therapeutic targets, biomarkers of response and autoimmune toxicity. We have published data on a proteomics approach using immunized sera and proteins from the vaccine cell lines as the proteome to identify proteins with biologic relevance to PDA. These serologic responses can be correlated to response as well as toxicity and identify potential therapeutic targets. This approach has identified a number of proteins including galectin-3 and annexin A2. Annexin A2 plays a role in pancreatic cancer invasion and antibodies against annexin A2 are therapeutic in a mouse model (Zheng, *et al*, 2011). We are now using an updated proteomics approach to improve on our selection of purified proteins isolated from our vaccine cell lines, with a goal of isolating the less abundant sero-reactive surface proteins and proteins in native conformation that are more likely to represent important functional PDA-associated proteins for therapeutics development. Our approach involves a strategy that couples the use of immuno-precipitation with SILAC (Gronborg, *et al*, 2006). SILAC is a quantitative proteomics method incorporating *in vivo* labeling of the proteins in the cell lysate followed by mass spectrometric analysis. We adapted SILAC for our studies because it "subtracts" out the proteins recognized by pre-vaccination sera from those recognized by post-vaccination sera, thereby allowing for enhanced detection of the proteins of interest. A vaccine cell population is cultured to incorporate nonradioactive "heavy" isotopes of lysine and arginine into its proteome instead of the usual "light" versions present in conventional growth medium. In parallel, another aliquot of cells are grown in "light" medium containing normal amino acids. After passaging, cultures are processed into "heavy" and "light" lysates, respectively. The pre-vaccine sera are used to immunoprecipitate proteins from light lysates and the post-vaccination sera from each patient are used to immunoprecipitate from heavy lysates. Both precipitates are compared by gel (1:1 ratio mixture) and by mass spectrometry for variances in isotopic ratios. Protein identified in bands that are higher in the post-vaccine sera immunoprecipitates are identified by mass spectrometry and confirmed by western blot. **Figure 8A** shows an example of the global changes in recognition of the pre- versus post-vaccine serum. Of the 825 proteins identified by mass spectrometry, 79 elicited a $\geq$2-fold increase in post-vaccine sera. Galectin-3 antibody recognition was 17-fold higher in the post-vaccine serum (**Figure 8B**) demonstrating the feasibility of this approach. **Figure 8C** compares pre- and post-vaccination antibody responses to glycoproteins isolated from the vaccine lines using lectins, using sera from two vaccinated patients to immunoblot relevant proteins. Arrows show serologic changes in protein detection pre- versus post-vaccination. The identity of these proteins is currently under investigation.

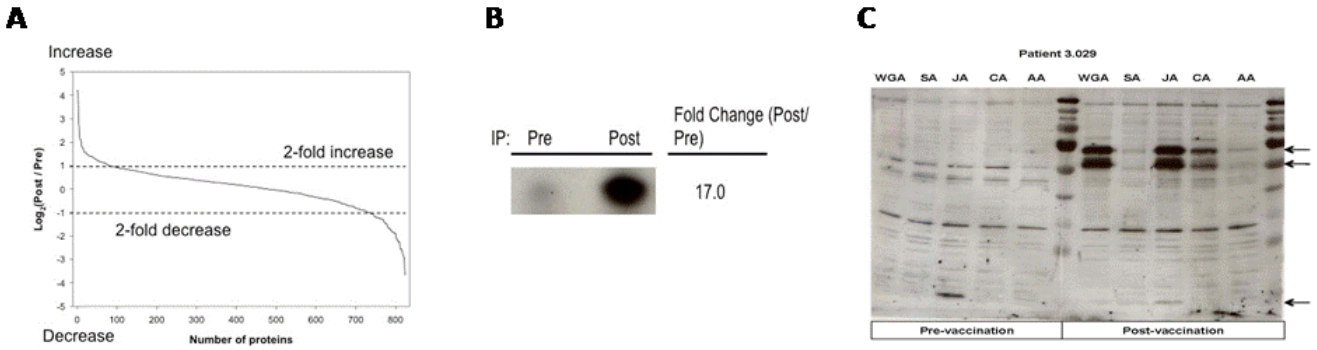


Figure 8.Successful use of SILAC to isolate membrane proteins. A. Global changes in antibody recognition post-3rd vaccination compared to pre-vaccination of patient 3.052. 825 proteins were quantitatively identified following immunoprecipitation with pre- and post-vaccine sera of pancreatic tumor cells grown in light versus heavy media (respectively). 79 proteins elicited at least a 2-fold increase in antibody response post-vaccination (post) as compared to pre-vaccination (pre).**B.** Validation of mass-spectrometry derived SILAC data using Western-blot for the known protein Galectin-3. Pre-vaccination (pre) and post-vaccination (post) antibodies were used for immunoprecipitation (IP). The IP proteins were separated by SDS-PAGE followed by Western blot for galectin-3. The fold-change detected by mass spectrometry is shown to the right of each blot. **C.** Different lectin preparations shown were used to purify glycoproteins from PDA cells. Shown are post sera recognition of glycoprotein bands (arrows).

Whole-exome sequencing to identify immune responsive genotypes. We are collaborating with the Ludwig Center for Cancer Genetics (PIs: Vogelstein and Diaz) to perform whole-exome sequencing using next-generation sequencing on DNA from the primary tumors and matched normal tissue from a subset of patients on the phase 1 study to compare long-term survivors versus non-responders in our cohort using methods previously described (Jones, *et al*, 2008). The data is not yet available but sample collection and similar analyses are planned for the proposed phase 2 study. As with all targeted therapies, we expect a subset of patients will respond to immunotherapy and there may be genetic determinants that define this response. These studies will define the genetic landscape of these tumors and may determine an 'immune responsive' phenotype. Furthermore, since each mutation is a potential neo-antigen that may drive an immune response, we will evaluate each mutation for antigenic potential in our model (Segal, *et al*, 2008).

Immunohistochemistry to characterize tumors and immune infiltrates. Tumors will also be tested for PD-L1 expression at baseline. We will collaborate with pathologists, Robert Anders and Janice Taube, to perform PD-L1 IHC. They have been instrumental in the development of this assay in completed and ongoing anti-PD-1 studies. Their work suggests that PD-L1 expression predicts response to anti-PD-1 (Brahmer, *et al*, 2010; Topalian, *et al*, 2012). However, PD-L1 is also upregulated in response to IFN-γ released by infiltrating T cells and could potentially be a predictor of response to any active immunotherapy. Pre and post-treatment tumor biopsies will also be analyzed for PD-1 and PD-L1 expression as well as infiltration of immune cells (effector T cells, Tregs, B cells, dendritic cells, etc). Emerging data suggest that CTLA-4 antibody has direct effects on Tregs. Characterization of immune checkpoint expression as well as immune infiltrates may be predictive of response to therapy and may also give insight into next generation combinatorial approaches. Preliminary data from the neoadjuvant study suggests that induction of a $T_h1$and T_h17 phenotype at the tumor itself predicts response. Furthermore, upregulation of other inhibitory molecules such as PD-1, PD-L1, IL-10, and TGF-β may identify other targets for combinatorial strategies.

9.3 Sample Collection

9.3.1 Research Blood Collection and Submission

One 10 ml yellow top tube (Catalog # BD-364606) collected prior to administration of the first dose of vaccine is required for HLA-typing. Eighteen 10 ml lavender/purple top tubes (Catalog # BD-366643) or 180cc heparinized syringes and two 10 ml serum separator tubes (SST) (Catalog # BD-366430) collected at the indicated time points are required for immune monitoring and serum banking respectively. Research blood samples should be shipped at room temperature FedEx priority overnight to Dr. Dung Le's laboratory.

The yellow and purple top tubes can be sent as they are drawn in FedEx shipping packages according to IATA regulations.

Procedure for Isolation of Serum

1) Serum separator tubes (SST) should be spun down within 1 hour after blood draw for best results. The blood in the SST should look deep red in color and thick in appearance.

2) Blood is to be at room temperature (18ºC - 25ºC); hold the centrifuge at room temperature prior to processing.

3) Invert SST 5-10 times immediately prior to spinning.

4) Place SST in the centrifuge and balance the rotor.

5) Spin SST in centrifuge at 2500 rpm for 10 minutes in swinging bucket (SW) or 15 minutes in a fixed angle (FA) rotor at room temperature (18ºC - 25ºC). Make sure that the centrifuge reaches speed and is maintained throughout the entire spin.

6) Carefully remove SST from centrifuge and visually inspect it for proper separation. If separation is not observed, repeat the spin one more time. Do not repeat more than once. If separation does not occur following the second spin, send it in its unseparated form.

7) Place SST in FedEx Clinical Pak and mark date and time it was spun down.

Shipping Instructions:
Please ship the samples using FedEx Clinical Paks and mark the checkbox on the FedEx Clinical Pak to confirm that "the shipment meets the definition of Biological Substance Category B packed in compliance with IATA Packing Instruction 650."

Please only obtain and ship the blood on a Monday, Tuesday, Wednesday or Thursday.
Samples cannot be drawn or shipped on a Friday or on the weekends.

Please notify Dr. Dung Le's Laboratory when you have a sample to be shipped. Be sure to ship FedEx priority overnight.

In case of any questions, please contact JHU laboratory personnel:
[redacted]

Shipping Address for Dr. Dung Le's Laboratory:
[redacted]

[redacted]

9.3.2 Archived Tumor Samples and Biopsies

Archived Tumors: Archived fine needle aspirate (FNA) biopsy samples do not contain sufficient tissue and do not need to be collected. In all other cases, blocks or slides should be sent to Dr. Dung Le's Laboratory.

[redacted]

If a block cannot be sent the protocol is as follows:

Slide Cutting Protocol -12 slides per block
Slides #1 and #12 to be regular 5 microns, Plus slides, H&E, with cover.
Slides #2-11 need to be UNSTAINED and 8 microns, Plus slides, NO COVERSLIP.
Blades need to be changed between blocks.
If possible, Slides and process need to be DNAse free.

Biopsies: Four to six core biopsies will be obtained. These tissue cores will be 18-22 gauge in diameter and at least 1cm in length. If four biopsies can be obtained, one may be frozen per standard protocols. Inability to obtain a biopsy with a reasonable attempt will not preclude treatment and the patient will remain eligible for all other translational components. The use of imaging to facilitate biopsies will be decided upon by the study physician and members of the interventional radiology team. Biopsy specimens should be embedded in paraffin. The shipping address is the same as above.

Sample Identification

Each biopsy slide will be labeled with the subject ID and a code indicating body site, study dose number. Possible body sites include P (Pancreas), N (Lymph node), LU (lung), LI (liver), B (Bone) O (other). The overall syntax for this code is shown in the following example: XXX-N-D1. This example indicates a lymph node biopsy performed on subject XXX prior to dose 1.

9.3.3 Diagnostic Tissue Samples

Tissue, fluid, or blood may be collected from standard of care procedures used to treat or diagnose immune related toxicities. These samples should be shipped to Dr. Dung Le's Lab (address can be found in section 9.3.1).

10. STUDY CALENDAR

Arm A Study Calendar

Baseline evaluations are to be conducted within 28 days prior to randomization unless otherwise indicated. Blood samples must be collected and analyzed at local or central labs within 4 days prior to dosing. Week 1 dosing should occur no sooner than 14 days after the last FOLFIRINOX dose and no later than 70 days after the last FOLFIRINOX dose. Please refer to **Section 6** for ipilimumab dose delays, skipping, and discontinuation rules.

Procedure	**Baseline (Day -28 to 0)**	**Wk 1**	**Wk 4**	**Wk 7**	**Wk 10**	**Wk 14**	**Wk 18**[18]	**Continuation of Therapy (every 8 weeks)**		**Off Study**[20]
								Day 1[18]	**Day 28**[19]	
Visit Windows (days)[17]	-	+7	+7	+7	+7	+7	+7	+7	+7	+/- 7
Vaccine		A	A	A	A			A		
Ipilimumab		B	B	B	B			B		
Informed consent	X									
Inclusion/exclusion criteria	X									
Demographics	X									
Medical history	X									
Concurrent meds	X	X	X	X	X	X	X	X	X	X
Physical exam[1]	X	X	X	X	X	X	X	X		X
Vital signs[2]	X	X	X	X	X	X	X	X		X
Height[3]	X									
Weight	X	X	X	X	X	X	X	X		X
Performance status[1]	X	X	X	X	X	X	X	X		X
Hematology profile[4, 10]	X	X	X	X	X	X	X	X	X	X
Chemistry profile[5, 10]	X	X	X	X	X	X	X	X	X	X
Autoimmune and Endocrine Panel[6, 10]		X	X	X	X	X	X	X	X	X
HIV/Hepatitis Panel[7]	X									
Cardiac Function Tests [22]	X									
Urinalysis & Microscopic Exam[8, 10]	X	X								
HCG[9]	X									
CA 19-9[10, 21]	X	X	X	X	X	X	X	X	X	X
HLA-typing		X								

Procedure	Baseline (Day -28 to 0)	Wk 1	Wk 4	Wk 7	Wk 10	Wk 14	Wk 18[18]	Continuation of Therapy (every 8 weeks)		Off Study[20]
								Day 1[18]	Day 28[19]	
Lactoferrin/WBC[11]		X								
Adverse event evaluation		X	X	X	X	X	X	X	X	X
Vaccine Site Assessment[12]			X	X	X	X	X	X	X	X
CT or MRI[13]	X	X			X		X	X		X
Tumor measurements[14]	X	X			X		X	X		X
Peripheral blood (up to 200cc)[10]	X		X	X	X	X	X	X		X
Serum (20cc)[10]	X		X	X	X	X	X	X		X
Archived Tumor Tissue[15]	X									
Tumor Biopsy[16]		X		X						

A: Pancreatic Tumor Vaccine will be administered prior to Ipilimumab.
B: Ipilimumab will be administered after vaccine.
1: Complete physical exam will be completed at baseline; focused physical examinations will be conducted thereafter. Exam and performance status may be done within 4 days prior to dosing and can be repeated prior to dosing, if needed.
2: Temperature, blood pressure, pulse, and oxygen saturation at baseline. Temperature, blood pressure, and pulse should be taken prior to ipilimumab, every 30 minutes during infusion and 1 hour after the end of infusion.
3. Height recorded prior to baseline period is acceptable, as height is not repeated frequently.
4: CBC with differential including absolute eosinophil count, absolute neutrophils, absolute lymphocytes, and platelets.
5: Albumin, amylase, lipase, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
6: Anti-nuclear antibody (ANA) and TSH. ANA to be done only prior to Week 1 treatment and later if clinically indicated.
7: HIV, hepatitis C antibody, and HBsAg.
8: Bilirubin, blood, glucose, ketones, leukocytes, nitrite, pH, protein, and specific gravity. Urinalysis should also be collected if clinically indicated.
9: Serum pregnancy test (women of childbearing potential).
10: Labs and research bloods may be collected within a window of up to 4 days prior to dosing and can be repeated prior to dosing, if needed.
11: Collected when available, any time after completing eligibility and prior to treatment. Values should also be collected if patients develop colitis.
12: Vaccine site reactions include, but are not limited to: erythema, induration, pruritis, tenderness, warmth, blisters, and vaccine site flares.
13: Spiral CT of thorax, abdomen, and pelvis (and other imaging studies as clinically indicated to evaluate suspected sites of metastatic disease). If a subject cannot have a CT scan (e.g., allergy to contrast dye), an MRI should be performed. The screening CT may serve as the Week 1 assessment if

performed within 28 days of study drug administration. CT scans required during treatment may be done within 2 weeks prior to scheduled visits.

14: RECIST 1.1 and irRC (**Appendix A**).

15: Attempts to obtain archival tumor samples will be made for every patient until the sample is obtained or documentation that the sample cannot be obtained. Fine needle aspirates will not be collected.

16: Tumor core biopsies (4-6) will be collected at Week 1 and 6 weeks from the 1st vaccine (or up to 1 week prior) only if a patient's tumor is thought to be reasonably safe and easy to biopsy). Additional optional biopsies may be obtained later in the course of therapy in responding patients. If biopsies are not obtained due to lack of funding, these omissions will not be considered protocol deviations. Biopsies at sites other than JHH are optional.

17: Delays up to 7 days at the discretion of the PI. Longer delays to be approved by the sponsor.

18: Continuation of therapy will be determined at Week 18; therefore, the Week 18 visit will also be Day 1 of the first continuation dose.

19: Day 28 AE, VSR, and concomitant medication evaluations may be done as part of a clinic visit or via phone call with the patient.

20: Patients who discontinue treatment should be contacted every 12 weeks to monitor overall survival. Information on other cancer therapies after discontinuation of study treatment will be collected. Patients will also receive annual evaluations (+/- 2 months) either at Hopkins or locally.

21: If CA19-9 is within normal range at both study baseline and diagnosis (or early into treatment), CA19-9 will not be required on study.

22: EKG and echocardiogram (ECHO) will be done for any patients with a history of congestive heart failure or at risk because of underlying cardiovascular disease or exposure to cardiotoxic drugs. For patients who develop evidence of CHF, MI, cardiomyopathy, or myositis while on study, cardiac evaluation including lab tests and cardiology consultations will be done as clinically indicated including EKG, CPK, troponin, and ECHO.

Arm A Study Calendar for Patients That Must Discontinue Ipilimumab Due to Toxicity

Blood samples must be collected and analyzed at local or central labs within 4 days prior to dosing. LFT results must be reviewed by the principal investigator (or designee) to meet the same dosing criteria specifications for ipilimumab (see Section 6.2).

Procedure	Wk 4		Wk 7		Wk 10		Wk 14	Wk 18[11]	Continuation of Therapy (every 8 weeks)			Off[13] Study
	Day 1	Day 2	Day 1	Day 2	Day 1	Day 2	Day 1	Day 1	Day 1[11]	Day 2	Day 28[12]	
Visit Windows (days)[1]	+7	-	+7	-	+7	-	+7	+7	+7	-	+7	+/- 7
Cyclophosphamide	A		A		A				A			
Vaccine		B		B		B				B		
Concurrent meds	X		X		X		X	X	X		X	X
Physical exam[2]	X		X		X		X	X	X			X
Vital signs[3]	X	X	X	X	X	X	X	X	X	X		X
Weight	X		X		X		X	X	X			X
Performance status[2]	X		X		X		X	X	X			X
Hematology profile[4, 6]	X		X		X		X	X	X		X	X
Chemistry profile[5, 6]	X		X		X		X	X	X		X	X
CA 19-9[6, 14]	X		X		X		X	X	X		X	X
Adverse event evaluation	X		X		X		X	X	X		X	X
Vaccine Site Assessment[7]	X		X		X		X	X	X		X	X
CT or MRI[8]					X			X	X			X
Tumor measurements[9]					X			X	X			X
Peripheral blood (up to 200cc)[6]	X		X		X		X	X	X			X
Serum (20cc)[6]	X		X		X		X	X	X			X
Tumor Biopsy[10]			X									

A: Cyclophosphamide (CY).
B: Pancreatic Tumor Vaccine.
1: Delays up to 7 days at the discretion of the PI. Longer delays to be approved by the sponsor.
2: Complete physical exam will be completed at baseline; focused physical examinations will be conducted thereafter. Exam and performance status may be done within 4 days prior to dosing and can be repeated prior to dosing, if needed.
3: Temperature, blood pressure, and pulse should be taken prior to CY and Vaccine and post-Vaccine administration.
4: CBC with differential including absolute eosinophil count, absolute neutrophils, absolute lymphocytes, and platelets.
5: Albumin, amylase, lipase, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
6: Labs and research bloods may be collected within a window of up to 4 days prior to dosing and can be repeated prior to dosing, if needed.
7: Vaccine site reactions include, but are not limited to: erythema, induration, pruritis, tenderness, warmth, blisters, and vaccine site flares.
8: Spiral CT of thorax, abdomen, and pelvis (and other imaging studies as clinically indicated to evaluate suspected sites of metastatic disease). If a subject cannot have a CT scan (e.g., allergy to contrast dye), an MRI should be performed. CT scans required during treatment may be done within 2 weeks prior to scheduled visits.
9: RECIST 1.1 and irRC (**Appendix A**).
10: Tumor core biopsies (4-6) will be collected at Week 1 and 6 weeks from the 1st vaccine (or up to 1 week prior) only if a patient's tumor is thought to be reasonably safe and easy to biopsy. Additional optional biopsies may be obtained later in the course of therapy in responding patients. If biopsies are not obtained due to lack of funding, these omissions will not be considered protocol deviations. Biopsies at sites other than JHH are optional.
11: Continuation of therapy will be determined at Week 18; therefore, the Week 18 visit will also be Day 1 of the first continuation dose.
12: Day 28 AE, VSR, and concomitant medication evaluations may be done as part of a clinic visit or via phone call with the patient.
13: Patients who discontinue treatment should be contacted every 12 weeks to monitor overall survival. Information on other cancer therapies after discontinuation of study treatment will be collected. Patients will also receive annual evaluations (+/- 2 months) either at Hopkins or locally
14: If CA19-9 is within normal range at both study baseline and diagnosis (or early into treatment), CA19-9 will not be required on study.

Arm B Study Calendar

Baseline evaluations are to be conducted within 28 days prior to randomization unless otherwise indicated.

Procedure	Baseline (Day -28 to 0)	Day 1 of each Cycle	Off Study +/- 14 days
FOLFIRINOX		X	
Informed consent	X		
Inclusion/exclusion criteria	X		
Demographics	X		
Medical history	X		
Concurrent meds	X		
Physical exam[1]	X		
Vital signs[2]	X		
Height[3]	X		
Weight	X		
Performance status	X		
Hematology profile[4]	X		
Chemistry profile[5]	X		
HIV/Hepatitis Panel[6]	X		
Urinalysis & Microscopic Exam[7]	X		
HCG[8]	X		
CA 19-9[13]	X	X	X
CT or MRI [9]	X	X	X
Tumor measurements[9, 10]	X	X	X
Peripheral blood (up to 200cc)[11]	X	X	X
Serum (20cc)[11]	X	X	X
Archived Tumor Tissue	X		
Tumor Biopsy (optional)[12]		X	

FOLFIRINOX: 5- Fluorouracil, irinotecan, leucovorin, and oxaliplatin

1: Complete physical exam will be completed at baseline
2: Temperature, blood pressure, pulse, and oxygen saturation.
3: Height recorded prior to baseline period is acceptable, as height is not repeated frequently.
4: CBC with differential including absolute eosinophil count, absolute neutrophils, absolute lymphocytes, and platelets
5: Albumin, amylase, lipase, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
6: HIV, hepatitis C antibody, and HBsAg
7: Bilirubin, blood, glucose, ketones, leukocytes, nitrite, pH, protein, and specific gravity
8: Serum pregnancy test (women of childbearing potential)
9: Spiral CT of thorax, abdomen, and pelvis (and other imaging studies as clinically indicated to evaluate suspected sites of metastatic disease). If a subject cannot have a CT scan (e.g., allergy to contrast dye), an MRI should be performed. Scans will be done at screening and week 10, then every 8 weeks and at off study visits. CT scans required while on study may be done within a window of +/- 2 weeks.
10: RECIST 1.1
11: Peripheral blood and serum to be collected at baseline, approximately week 10 (+/- 2 weeks), and at Off Study.
12: Optional tumor biopsies to be taken (if a patient's tumor is thought to be reasonably safe and easy to biopsy) prior to first dose of FOLFIRINOX on study and 5 - 6 weeks later. Additional optional biopsies may be obtained later in the course of therapy in responding patients.
13: CA19-9 tests to be done every 4-6 weeks. If CA19-9 is within normal range at both study baseline and diagnosis (or early into treatment), CA19-9 will not be required on study.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009] and the immune related Response Criteria (irRC) [Appendix A]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with ipilimumab or pancreatic tumor vaccine.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which

greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

11.1.3 RECIST Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray or as ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions,

short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.1.4 RECIST Response Criteria

11.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status

change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.1.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

∗See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
***In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*

Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

11.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.1.6 Progression-Free Survival (PFS)

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Management

All information will be collected on study-specific case report forms (CRFs) by study staff. These data will be reviewed for completeness and accuracy by the Principal Investigator. The Sidney Kimmel Comprehensive Cancer Center Clinical Research Office will monitor JHU study patients, while UCSF will use its internal CRO to monitor its study patients. Eligibility for both sites will be monitored by the SKCCC CRO as well.

External sites are responsible for submitting CDUS data and/or data forms to the Coordinating Center quarterly by December 31, March 30, June 30 and September 30 to allow time for Coordinating Center compilation, Principal Investigator review, and timely submission to CTEP (see Section 12.11). For trials monitored by CTMS, the monthly data submission to CTEP from Theradex should be copied to the Coordinating Center.

The Coordinating Center is responsible for compiling and submitting CDUS data to CTEP

for all participants and for providing the data to the Principal Investigator for review.

12.2 Safety Meetings

Scheduled meetings will take place weekly and will include the protocol principal investigator, study coordinator(s), data manager(s), sub-investigators (as appropriate), collaborators (as appropriate), and biostatisticians (as appropriate) involved with the conduct of the protocol. During these meetings matters related to the following will be discussed: safety of protocol participants, validity and integrity of the data, enrollment rate relative to expectation, characteristics of participants, retention of participants, adherence to protocol (potential or real protocol violations), data completeness, and progress of data for objectives.

12.3 Monitoring

This is a DSMP Level III study under the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center (SKCCC) Data Safety Monitoring Plan (DSMP, 12/6/2012, **Appendix J**). The protocol will be internally monitored by Dr. Dung Le. External data monitoring will be performed by the SKCCC Clinical Research Office Quality Assurance Program (CRO QA) at least quarterly, but may occur more or less frequently depending on the rate of accrual (per the DSMP). Additional data and safety monitoring oversight will also be performed by the SKCCC Safety Monitoring Committee (SMC - as defined in the DSMP) and a Medical Expert Committee (MEC) as detailed below.

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP web site (http://ctep.cancer.gov).

Authorized representatives of the Coordinating Center may visit the satellite site (UCSF) to perform audits or inspections, including source data verification. The purpose of these audits or inspections is to systematically and independently examine all trial-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), and any applicable regulatory requirements.

The Medical Expert Committee (MEC) for this clinical study contains three medical oncologists from other disciplines who are not affiliated with this clinical trial protocol. The MEC will review safety data on at least a semi-annual basis. The MEC will provide a written summary of each assessment to the IND Sponsor-Investigator after each meeting. In turn, the study team will forward these summaries to the JHU and UCSF IRB, and JHU SKCCC SMC. The operating plan of the MEC will be as follows:

- Meetings will be held at least semi-annually, and potentially more frequently if needed.

- Meetings will be conducted in-person or via video/teleconference, with a participant sign-in sheet collected at each meeting.
- Approximately one week prior to each MEC meeting, the study team will submit the following items to MEC personnel for review and discussion at the meeting (The PI may join the MEC meeting in order to answer any questions the MEC might have):
    - A summary of the clinical trial's progress to date;
    - The latest IRB-approved consent document;
    - A summary of all adverse events, serious adverse events, deaths, and withdrawals to date;

Note that the MEC reserves the right to halt trial accrual or all study activity if, after review, serious safety concerns warrant this action. If the MEC halts study accrual or all study activity, then the study team must notify the JHU SKCCC SMC, JHU and UCSF IRB, and the FDA immediately.

12.4 Collaborative Agreement

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed

combination protocol.

b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

Primary objective: To compare the overall survival of patients with metastatic pancreatic cancer with stable disease on FOLFIRINOX who then receive ipilimumab and the allogeneic GM-CSF transfected pancreatic tumor vaccine to patients who continue to receive FOLFIRINOX.

Secondary objectives: To evaluate safety and characterize toxicities, specifically immune-related adverse events, of ipilimumab in combination with pancreatic tumor vaccine in patients with metastatic pancreatic adenocarcinoma, to assess progression-free survival (PFS) and immune-related PFS, and duration of response in patients receiving treatment, to assess the objective response rate by RECIST and immune-related response criteria in patients receiving treatment, and to measure tumor marker kinetics (CA 19-9) in patients receiving treatment.

Exploratory objectives: To collect peripheral blood lymphocytes and serum to identify potential therapeutic targets and biomarkers and predictors of response and autoimmune toxicity. We will correlate induction of antigen specific T cell responses to mesothelin and changes in mesothelin-specific T cell epitope repertoire with OS. We will test if telomere length of lymphocytes can serve to help predict response. Induction of galectin-3 antibody responses will be correlated with response. Proteomic approaches will be used on pre and post treatment sera to identify targets and biomarkers of response or toxicity. To collect archived tissue and pre and post treatment biopsies to test for predictors of response and future targets for combinatorial therapy. Next generation genome sequencing will be used to identify immune responsive disease subtypes and immunohistochemistry will be used to characterize the nature of tumors and immune infiltrates in responsive subsets. Furthermore, upregulation of immune inhibitory molecules in the pre or post treatment samples may identify additional therapeutic targets.

13.2 Sample Size/Accrual Rate

Sample size. OS will be measured from the time of randomization after approximately 4-6 months of FOLFIRINOX until death. Individuals lost to follow-up will be censored at their last known visit. In the FOLFIRINOX study, approximately 53% of those alive at 6 months survived an additional 6 months. Assuming an accrual period of 24 months with a minimum follow-up of 12 months, 92 patients (46 per arm) provide 82% power to detect

an HR of 1.65 from the null rate of 53% at 6 months with a 1-sided type 1 error rate of 10%, i.e. an increase in the percent alive at 6 months from 0.53 for the FOLFIRINOX arm to 0.68 for the IPI/Vaccine arm. The projected accrual rate is 3.8 patients per month. Based upon these rates, a total of 75 deaths (34 in the IPI/Vaccine arm and 41 in the FOLFIRINOX arm) are needed.

13.3 Stratification Factors

Patients will be stratified based on the number of cycles of FOLFIRINOX (8 cycles or > 8 cycles) and by center.

13.4 Analysis of Secondary Endpoints

Time-to-event outcomes such as overall survival will be summarized using Kaplan-Meier estimates of survival function. Comparisons between treatments and subgroups of interest will be made using log-rank tests or Cox proportional hazards models. Binary outcomes will be summarized using proportions with exact 95% confidence intervals. Continuous outcomes will be summarized using means with standard deviations and 95% confidence intervals (or medians and inter-quartile ranges if appropriate). Comparisons between groups will be made using logistic regression and linear regression for binary and continuous variables. Non-parametric alternatives (e.g. Fisher's exact test or Kruskal-Wallis tests) will be considered as needed. Specific toxicities will tabulated by grade.

For correlative studies, continuous variables will be summarized with means or medians 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 both pre and post administration of each treatment. Plots will be used to show the changes in immune response over time both for each individual and for each arm. For each treatment, comparisons in the pre and post-treatment responses will be compared using paired t-tests (or Wilcoxon signed rank tests if appropriate) for continuous variables and Fisher's exact tests for dichotomous or categorical variables. Associations between immune parameters will be explored graphically (e.g. scatterplots, boxplots) and numerically (e.g. correlations, $\chi 2$ tests). Regression techniques (linear, logistic, linear mixed effects) will be used to explore the differences between the treatment arms.

We plan to examine the entire cohort as a whole as well as within the ipilimumab dose subsets (10 mg/kg and 3 mg/kg). We will use a test of interaction to determine whether or not the relationship between the two treatment arms differs significantly for the 10mg/kg and 3 mg/kg dose cohorts. If the test of interaction is not significant, then the primary analysis will pool both cohorts. If the test of interaction is significant, then the primary analysis will examine the cohorts separately. However, it should be noted that we have limited power to detect such an interaction with the current sample size. Therefore, it will be important to summarize the behavior within each ipilimumab dose level regardless of the significance of the test of interaction to help guide future trial development.

13.5 Reporting and Exclusions

13.5.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with ipilimumab and the pancreatic tumor vaccine.

13.5.2 Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

13.6 Stopping Guidelines

A single interim futility analysis will be performed once 50% of the information is collected, i.e. once 38 deaths are observed. We expect this to occur between 18-20 months after the start of randomization. The hazard ratio comparing the IPI/Vaccine arm to the FOLFIRINOX arm will be calculated. If the hazard ratio is greater than 1, i.e. the IPI/Vaccine arm is superior, then the trial will continue. If the hazard ratio is less than or equal to 1, i.e. the IPI/Vaccine arm is not superior, then consideration will be given for terminating the trial early for futility. Under the null hypothesis (i.e. both treatments are equally effective), the probability of stopping early would be 50%. The probability for stopping early when the true HR was 1.65 and 1.80 would be 6% and 3.5%, respectively.

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APPENDIX A IMMUNE RELATED RESPONSE CRITERIA (irRC)*

*Note that the proposed irRC have been incorporated as secondary end points in addition to standard criteria and evaluate alternative patterns of response in various disease setting and treatment regimens.

Immune Related Response Criteria

For all patients who experience disease progression on study, the date noted for of disease progression is the time of the scan where it is originally detected, and not the following date of the confirmatory scan.

Definitions of measurable and non-measurable disease

Measurable disease: Neoplastic masses that can be precisely measured in 2 in-plane perpendicular diameters. Both its longest diameter and its longest perpendicular must be greater than or equal to 10 mm. Lymph nodes must have a short-axis line-length of ≥ 15 mm. Malignant lymph nodes must be measurable in 2 perpendicular diameters. Both its longest diameter and its longest perpendicular must be greater than or equal to 15 mm. The quantitative endpoint will be defined as the product of the longest diameter with its longest perpendicular.

Non-measurable disease: Non-measurable lesions are those that are not suitable for quantitative assessment over time. These include:

1) Neoplastic masses that are too small to measure, because their longest uninterrupted diameter or longest perpendicular are less than 10 mm.

2) Neoplastic masses whose boundaries cannot be distinguished. This includes masses which cannot be demarcated from surrounding tissue because of inadequate contrast, masses with overly complex morphology, or those with highly heterogeneous tissue composition.

3) Other types of lesions that are confidently felt to represent neoplastic tissue, but difficult to quantify in a reproducible manner. These include bone metastases, leptomeningeal metastases, malignant ascites, pleural/pericardial effusions, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, ill-defined abdominal masses, etc.

For irRC, only target lesions selected at baseline and measurable new lesions are taken into account.

At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all **index lesions** (five lesions per organ, up to 10 visceral lesions and five cutaneous index lesions) is calculated.

At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (≥ 5 X 5 mm; up to 5 new lesions per organ: 5 new cutaneous lesions and 10 visceral lesions) are added together to provide the total time-point **tumor burden.**

Overall response using irRC:

- **Complete Response (irCR):** Complete disappearance of all tumor lesions (whether measureable or not, and no new lesions). CR must be confirmed by repeated, consecutive assessments made no less than 4 weeks from the date first documented.
- **Partial Response (irPR):** Decrease in SPD of 50% or greater by a consecutive assessment at least 4 weeks after first documentation.
- **Stable Disease (irSD):** Failure to meet criteria for irCR or irPR, in absence of irPD.
- **Progressive Disease (irPD):** At least 25% increase in SPD relative to nadir (minimum recorded tumor burden) Confirmation by a repeat, consecutive assessment no less than 4 weeks from the data first documented.

Table: Immune-Related Response Criteria Definitions

Index Lesion Definition	Non-Index Lesion Definition	New Measurable Lesions	New Unmeasurable Lesions	Percent change in tumor burden (including measurable new lesions when present)	Overall irRC Response
Complete Response	Complete Response	No	No	-100%	irCR
Partial Response	Any	Any	Any	≥ -50%	irPR
				<-50% to <+25%	irSD
				≥ +25%	irPD
Stable Disease	Any	Any	Any	< -50% to < +25%	irSD
				≥ +25%	irPD
Progressive Disease	Any	Any	Any	≥ +25%	irPD

Please note other key differences between irRC and the original WHO criteria:

New measurable lesions will be incorporated into the SPD

New non measurable lesions do not define progression but preclude irCR

Non-index lesions contribute to defining irCR (complete disappearance required).

Immune-Related Best Overall Response Using irRC (irBOR)

irBOR is the best confirmed irRC overall response over the study as a whole, recorded between the date of first dose until the last tumor assessment before subsequent therapy (except for local palliative radiotherapy for painful bone lesions) for the individual subject in the study. For the assessment of irBOR, all available assessments per subject are considered.

irCR or irPR determinations included in the irBOR assessment must be confirmed by a second (confirmatory) evaluation meeting the criteria for response and performed no less than 4 weeks after the criteria for response are first met.

REFERENCE

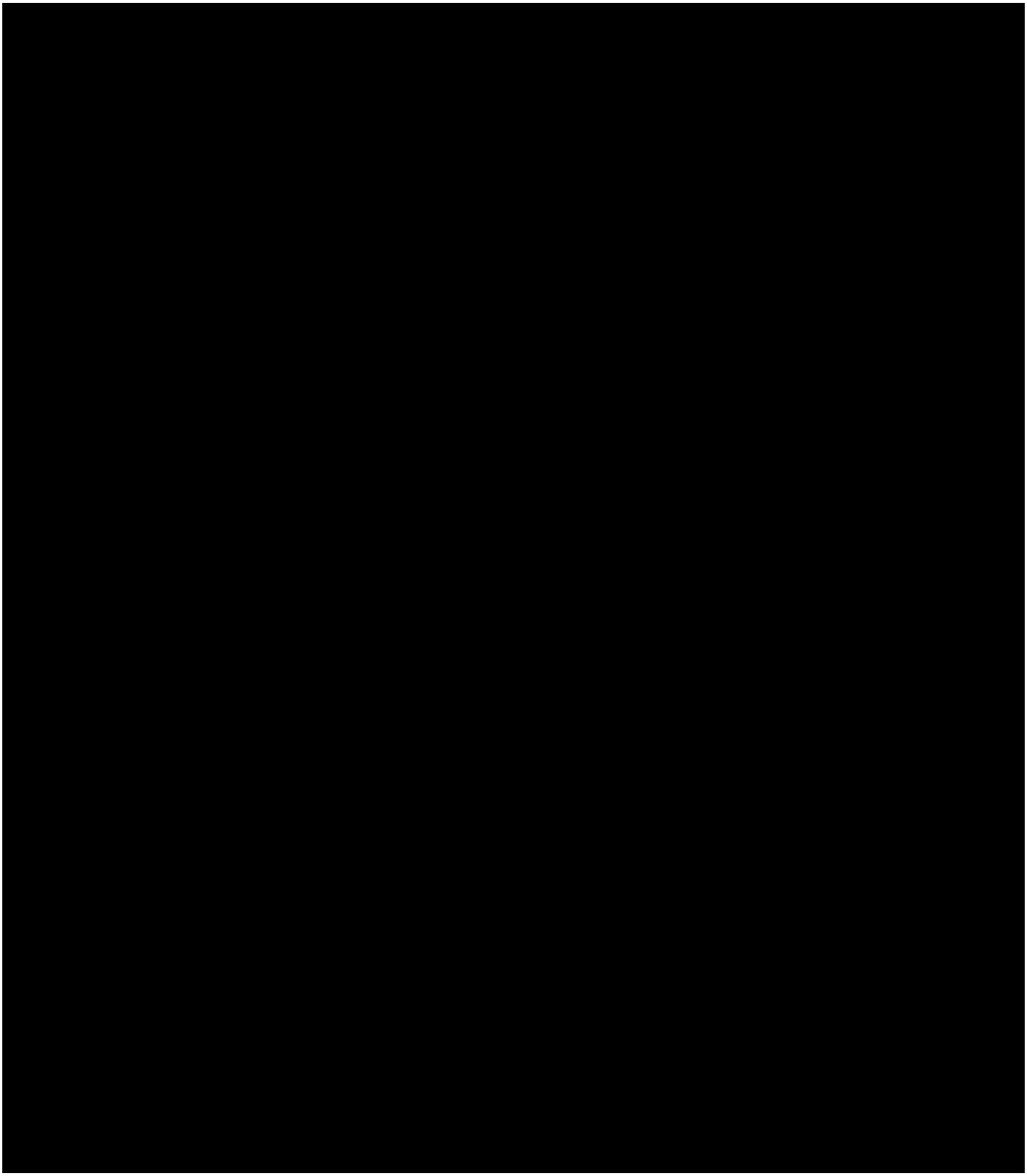
IrRC for the current protocol is adopted from the following reference:

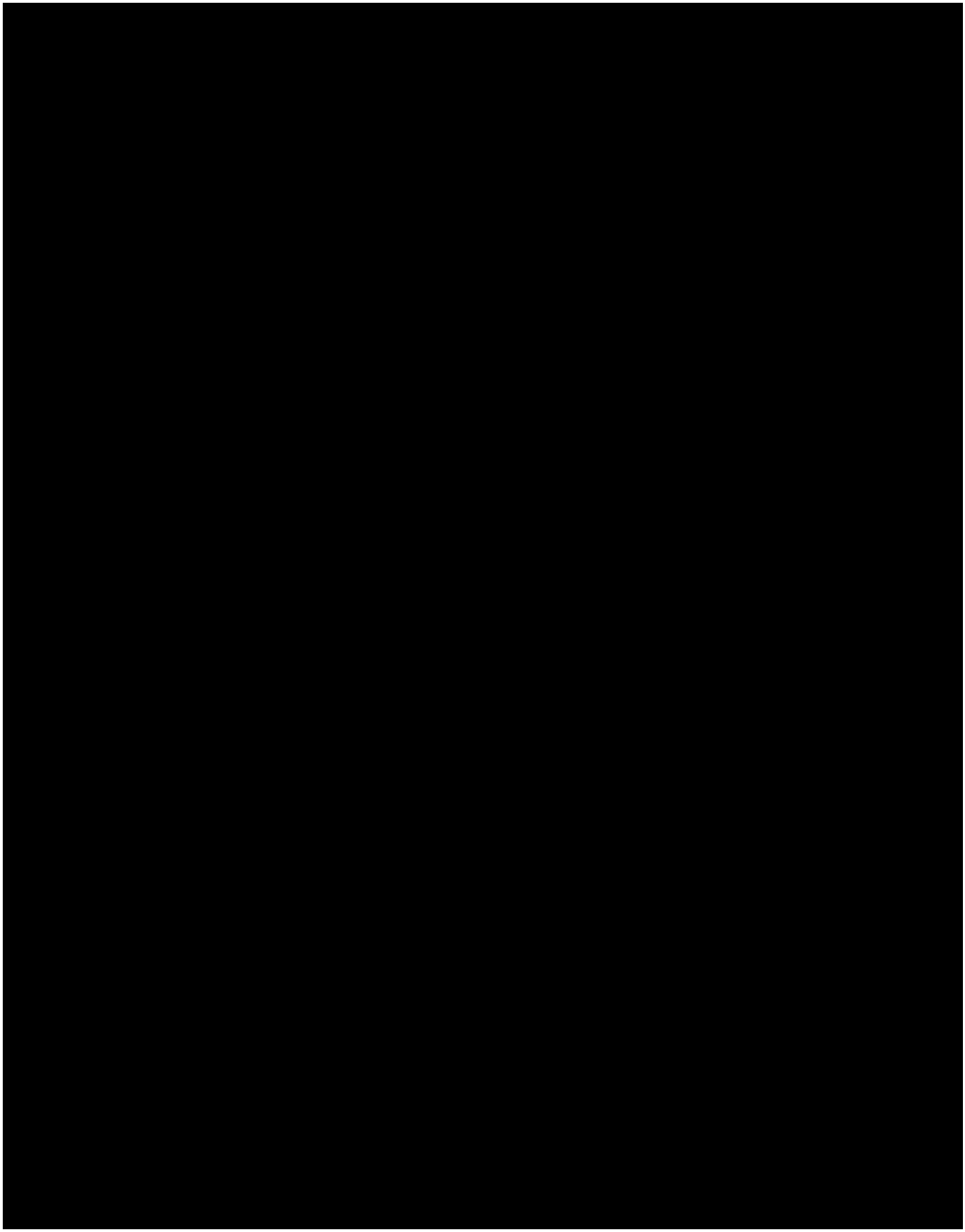
Wolchok, JD, Hoos, A, O'Day S, et al., Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria. Clinical Cancer Research, 2009 Dec 1;15(23):7412-20. Epub 2009 Nov 24.

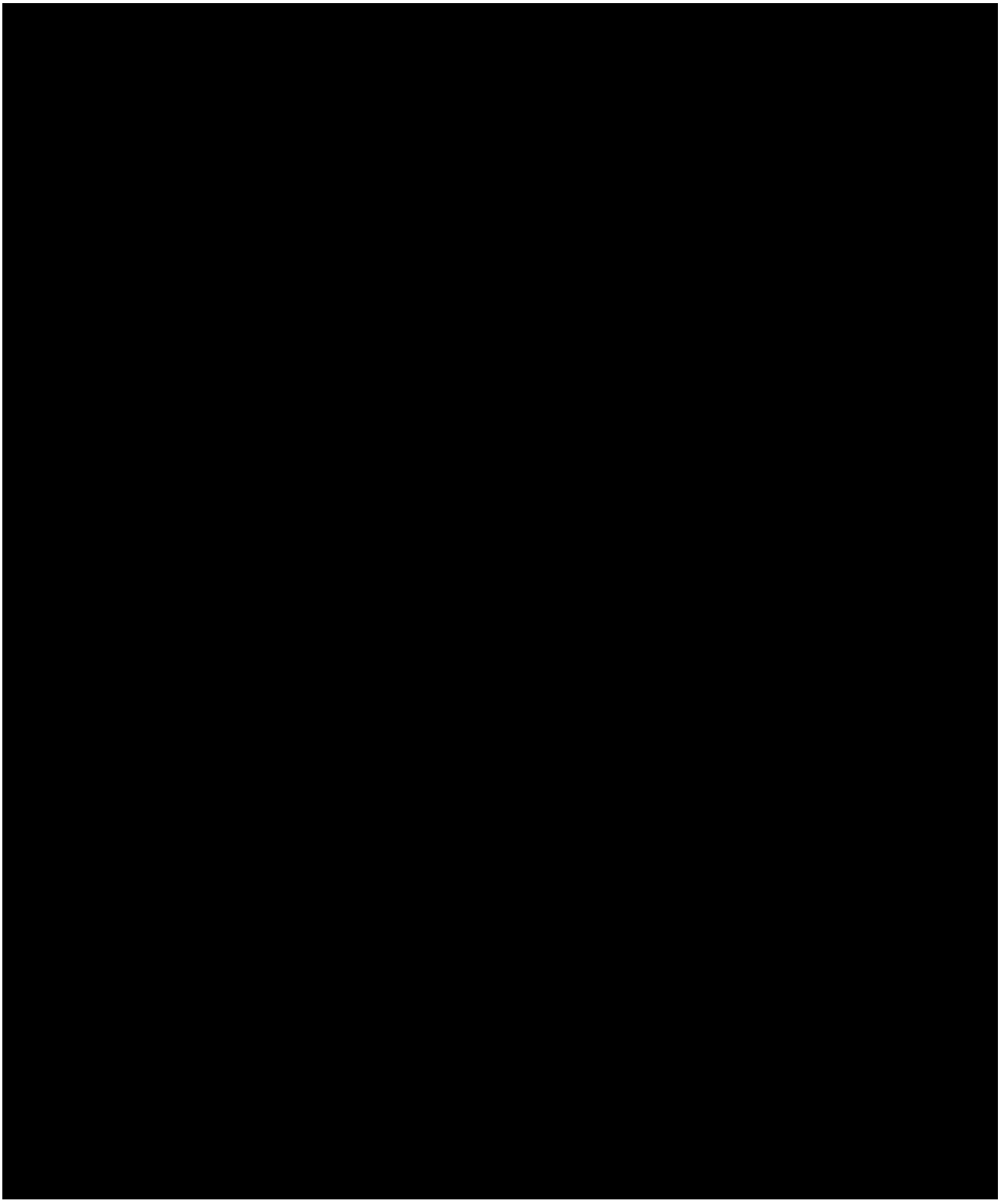
APPENDIX B PERFORMANCE STATUS CRITERIA

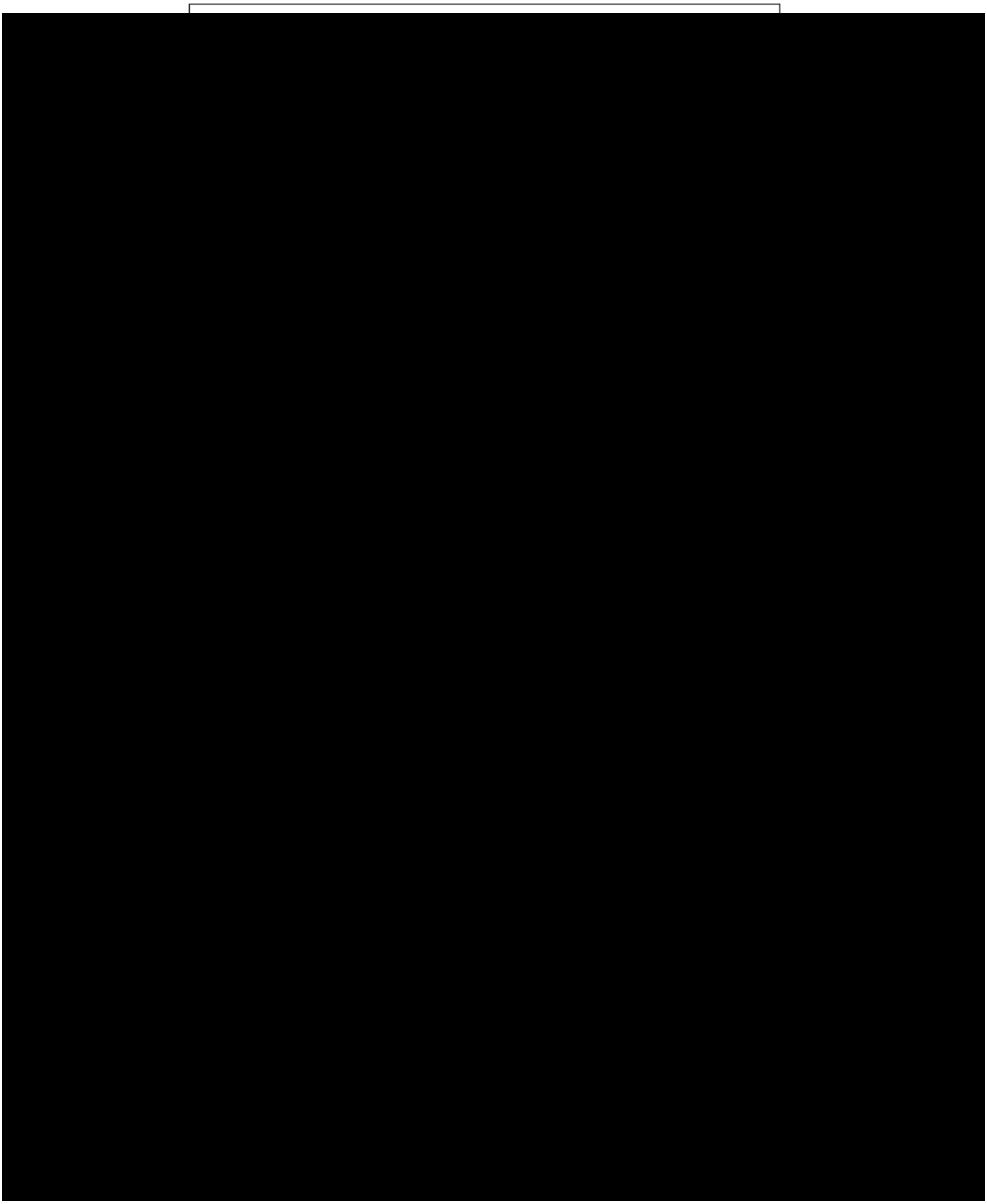
ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

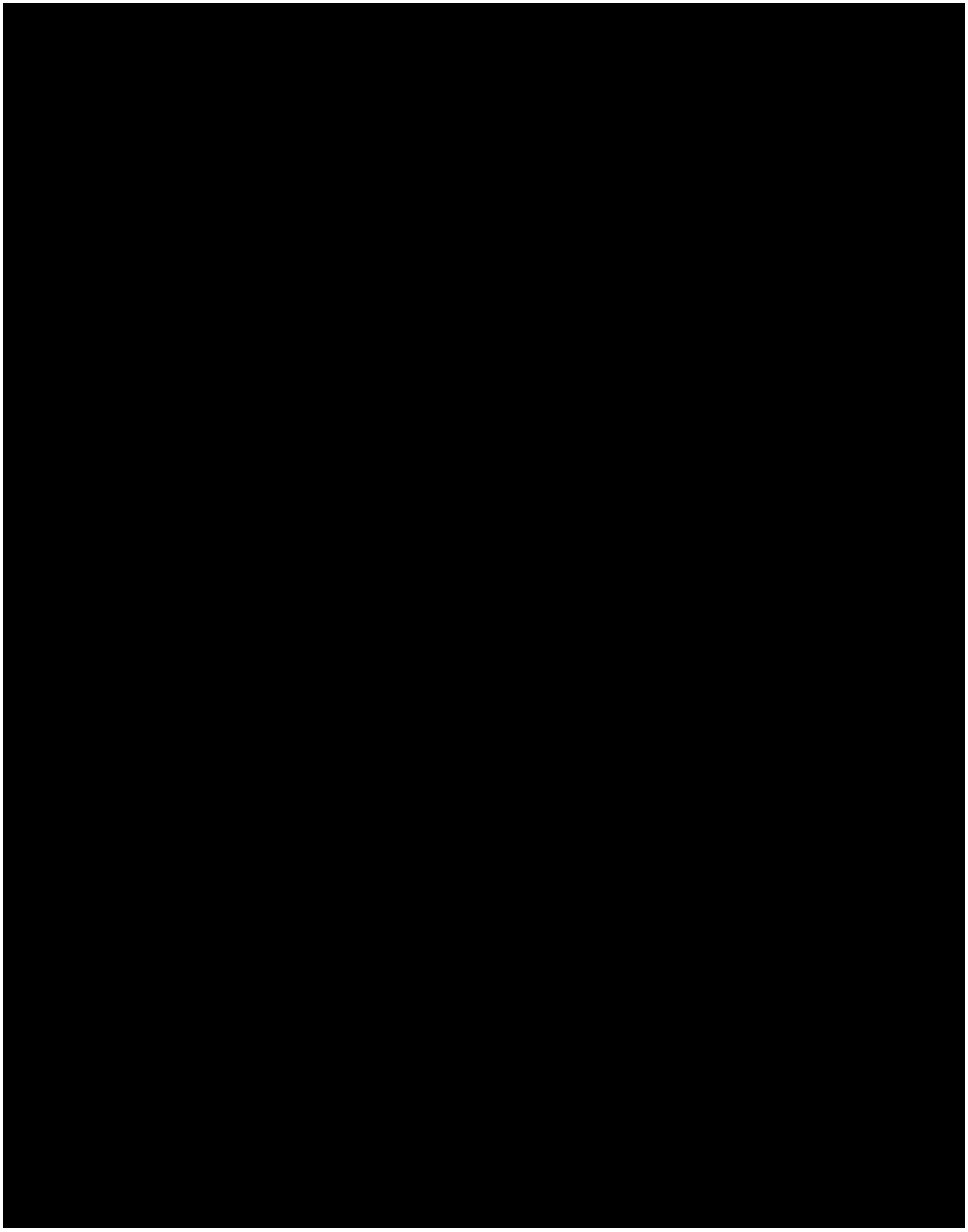
APPENDIX C MANAGEMENT OF IMMUNE-RELATED ADVERSE EVENTS, DIARRHEA, HEPATOTOXICITY, ENDOCRINOPATHY, AND NEUROPATHY*











APPENDIX D SAE REPORTING FORM TO SPONSOR

Serious Adverse Event Reporting Form

Please notify Dr. Jaffee, Dr. Le, and the coordinating center within 24 hours
[redacted]

Protocol Title:	**A Phase 2, Multicenter Study of FOLFIRINOX Followed by Ipilimumab in Combination with Allogeneic GM-CSF Transfected Pancreatic Tumor Vaccine in the Treatment of Metastatic Pancreatic Cancer**			
Protocol Number:	**Principal Investigator:**	**Signature of PI:**		**Date:**
Report Date:	**Hospital Admission Date:**	**Hospital Discharge Date:**	**Date of Discovery of Event:**	**Report Type:** ☐ Initial ☐ Follow-up ☐ Final Follow-up ☐ Death ☐ Addendum to:

Section A: Subject Information

Subject ID:	**Subject Initial:**	**Subject Gender:** ☐ Male ☐ Female

Section B: Event Information

Event diagnosis or symptoms:	**Date of First Dose (ipi + vaccine):**	**Action taken with the study drug (ipi + vaccine):** ☐ None ☐ Interrupted ☐ Discontinued
	Date of Last Dose (ipi + vaccine) prior to Event:	
	Number of Total Doses (ipi + vaccine):	

Event Onset Date:	**Event End Date:**

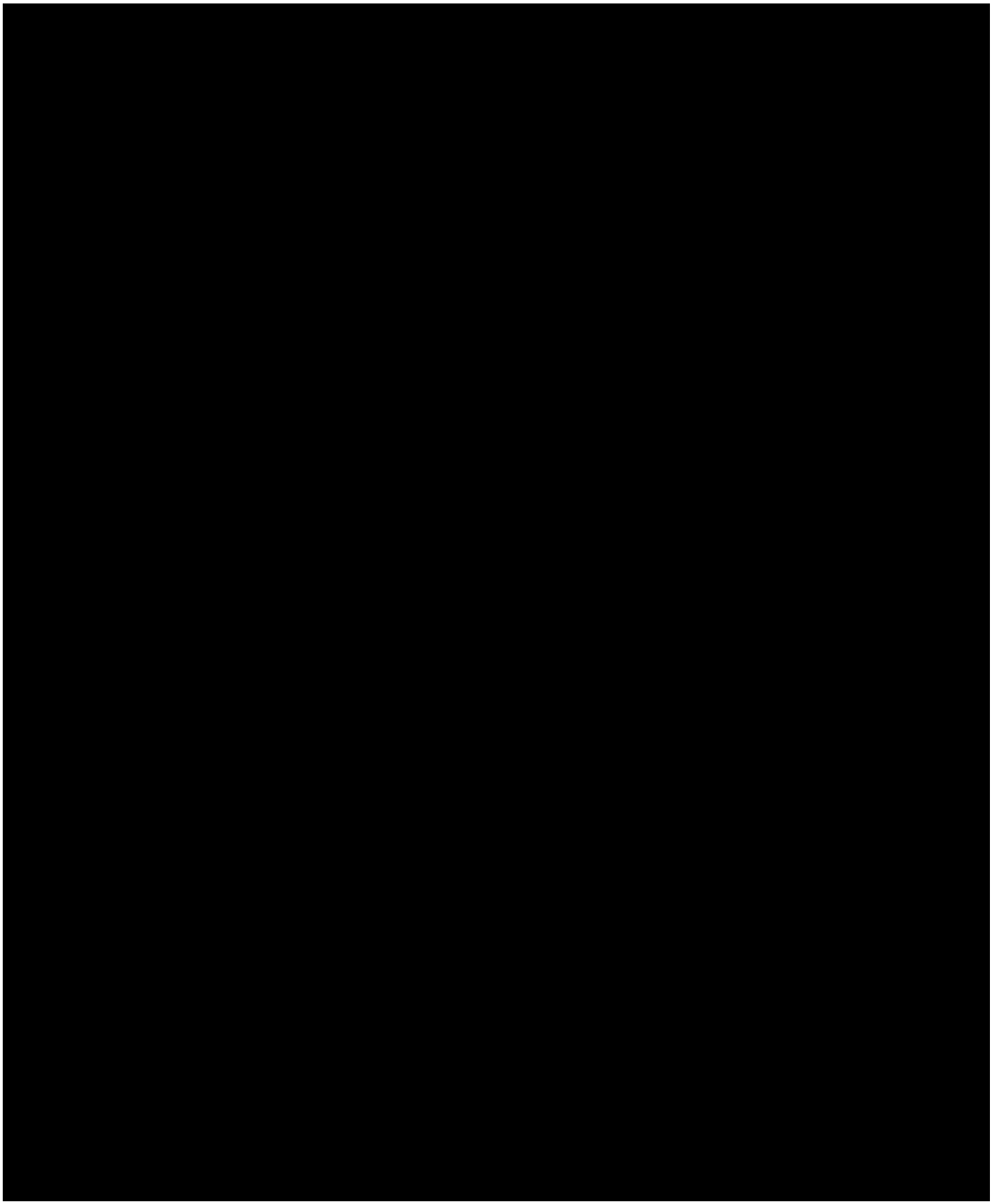
Relationship to:	**Ipilimumab**	**Vaccine**	**Cyclophosphamide**	**Underlying Disease**
Unrelated	☐	☐	☐	☐
Probably Unrelated	☐	☐	☐	☐
Possible Related	☐	☐	☐	☐
Probably Related	☐	☐	☐	☐
Definitely Related	☐	☐	☐	☐

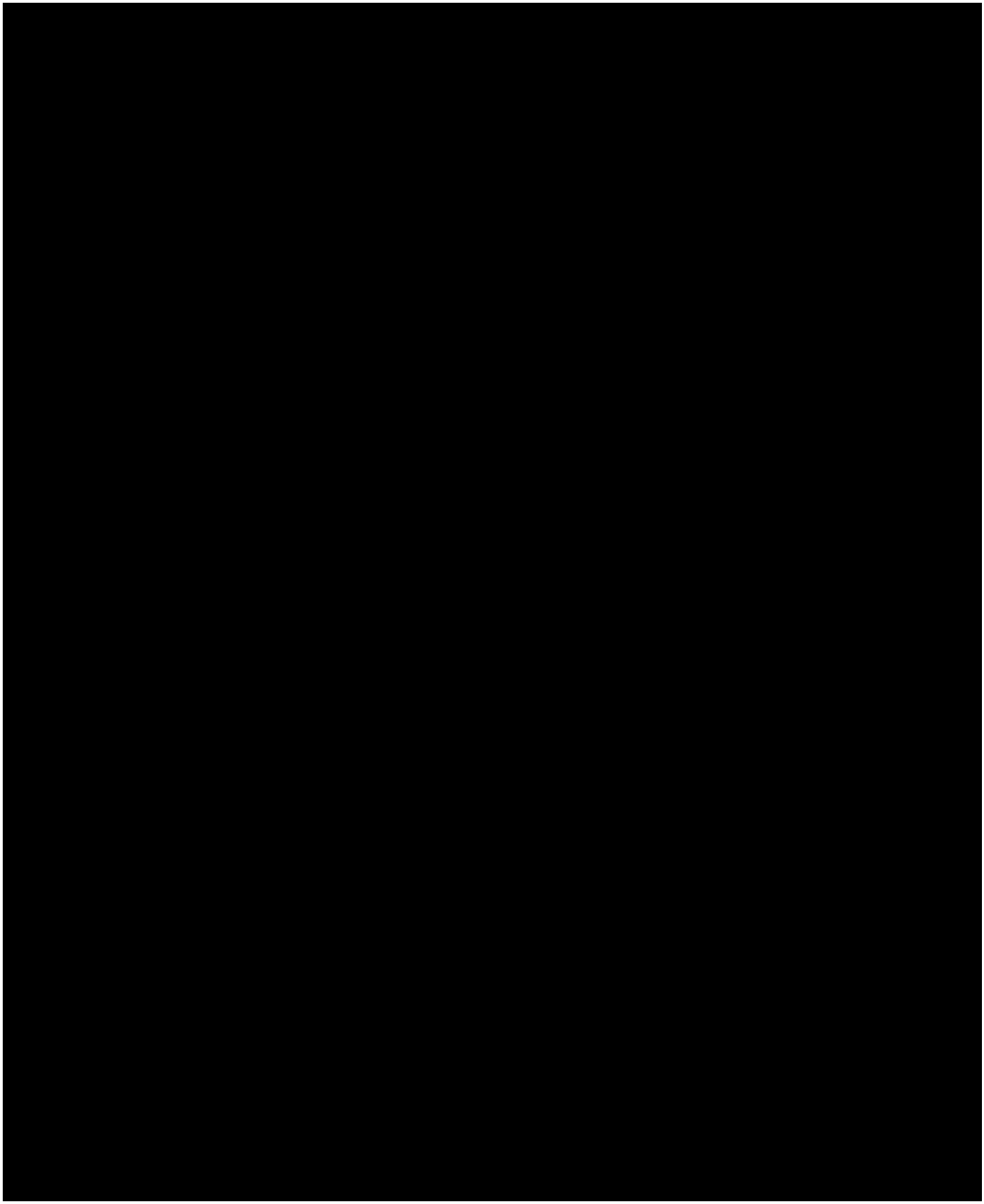
Section C: Brief Description of the Event:
Section D: Relevant Medical History
Section E: Concomitant Drug (Not related to SAE)

Name of the Drug	**Start Date**	**Stop Date**	**Route**	**Dose**	**Frequency**

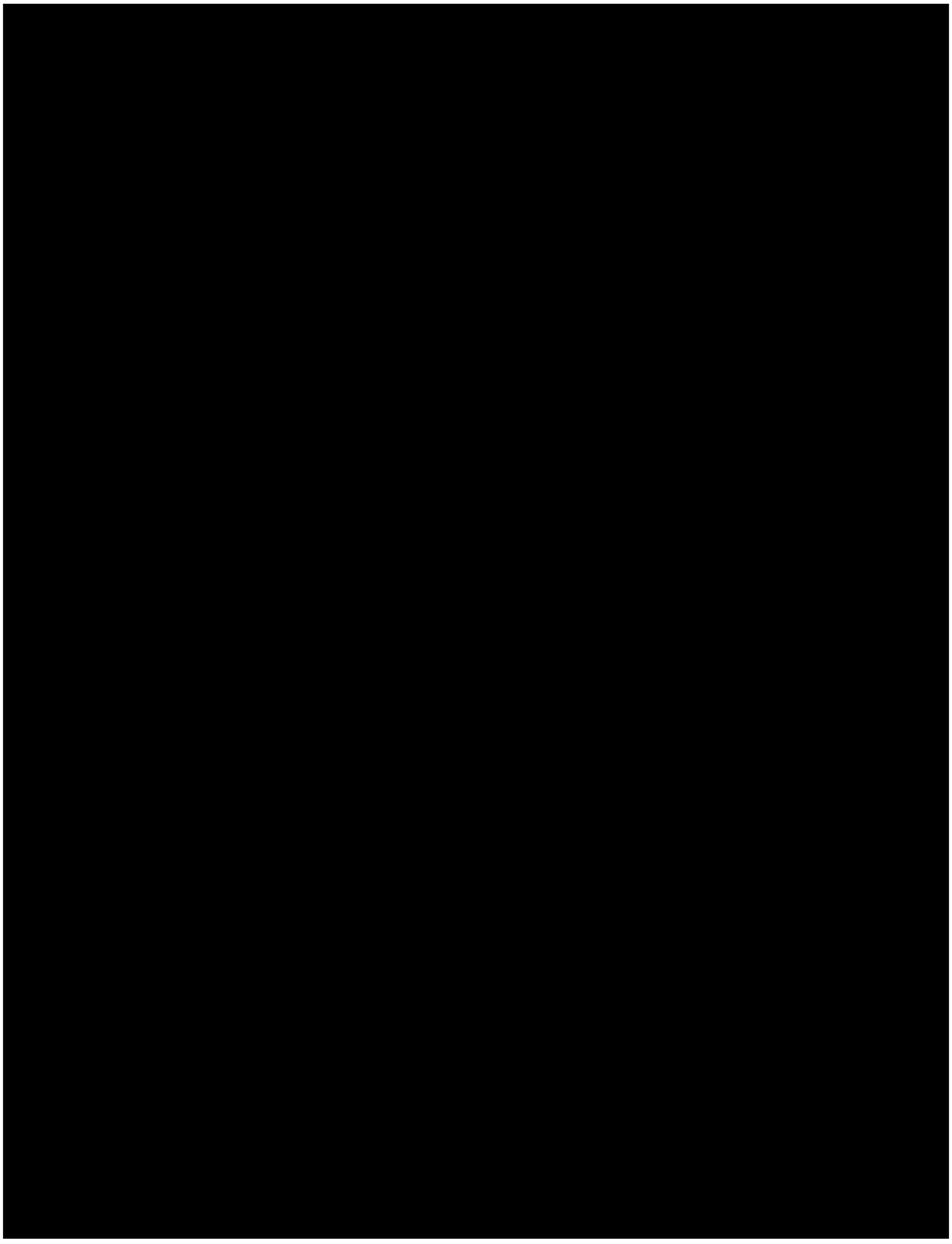
Section F: Comments
Additional Documents: ☐ Please specify

APPENDIX E **CAEPR FOR IPILIMUMAB**





APPENDIX F **RISK PROFILE FOR IPILIMUMAB**



APPENDIX G **RISK PROFILE FOR THE PANCREATIC TUMOR VACCINE**

APPENDIX H RISK PROFILE FOR FOLFIRINOX

5-fluorouracil

Common side effects: Diarrhea, nausea, vomiting, anorexia, stomatitis, esophagopharyngitis, leukopenia, anemia, dermatitis, and nail changes.

Less common side-effects: Thrombocytopenia, sensitivity to the sun, irritation of the eyelids or eyes, increased tearing of the eyes and runny nose, dryness, redness, tingling, pain, cracking of skin of the palms and soles, rash, darkening of the skin, especially the palms and soles and nail beds, and alopecia.

Rare but clinical important side-effects: Myocardial ischemia, angina, gastrointestinal ulceration, and bleeding.

Leucovorin

Common side effects: Leukopenia, nausea, vomiting, diarrhea, stomatis, alopecia, and dermatitis.

Less common side-effects: Thrombocytopenia, infection, fatigue, anorexia, constipation, and allergic reactions.

Oxaliplatin

Common side effects: peripheral neuropathy, nausea which may be accompanied by vomiting, diarrhea, constipation, neutropenia, anemia, thrombocytopenia, fatigue, fever, headache, rhinitis, and insomnia.

Less common side-effects: Allergic reaction with redness of the face, itching, hives, a sensation of tightening in the throat or airway, elevated AST, elevated ALT, elevated bilirubin, edema, cough, and dyspnea.

Irinotecan

Common side effects: Nausea, vomiting, abdominal pain, diarrhea, constipation, anorexia, mucositis, neutropenia, leukopenia (including lymphocytopenia), anemia, thrombocytopenia, asthenia, pain, fever, infection, abnormal bilirubin, and alopecia.

Less common side-effects: Constipation, runny nose and eyes, flushing, sweating, difficulty speaking, slurred speech and swollen tongue during or right after irinotecan administration, stomach cramping, early diarrhea occurring during or right after the irinotecan administration, skin rash, trouble sleeping, and shortness of breath.

APPENDIX I **RISK PROFILE FOR CYCLOPHOSPHAMIDE**

Common side-effects

- Leukopenia (including lymphocytopenia)
- Anorexia,
- Nausea,
- Vomiting,
- Fatigue
- Alopecia

Less common side-effects

- Hyponatremia,
- Early menopause,
- Hematuria, and
- Pain of the bladder, liver, lungs, and veins

Rare but clinical important side-effects

- Carcinogenicity (bladder and skin cancers, leukemia)
- Hives
- Blurry vision
- Numbness and tingling of the mouth and throat
- Scarring of the lung

APPENDIX J SKCCC AT JOHNS HOPKINS DATA SAFETY MONITORING PLAN (DSMP)