Official Title: A Phase II Study of GM-CSF secreting allogeneic pancreatic cancer vaccine in combination with PD-1 Blockade Antibody (Pembrolizumab) and Stereotactic Body Radiation Therapy (SBRT) for the Treatment of Patients with Locally Advanced Adenocarcinoma of the Pancreas

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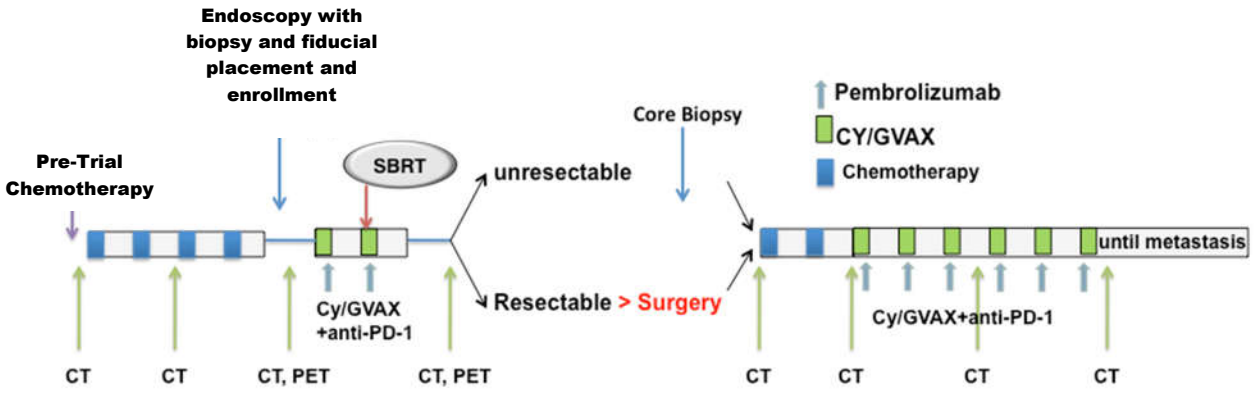
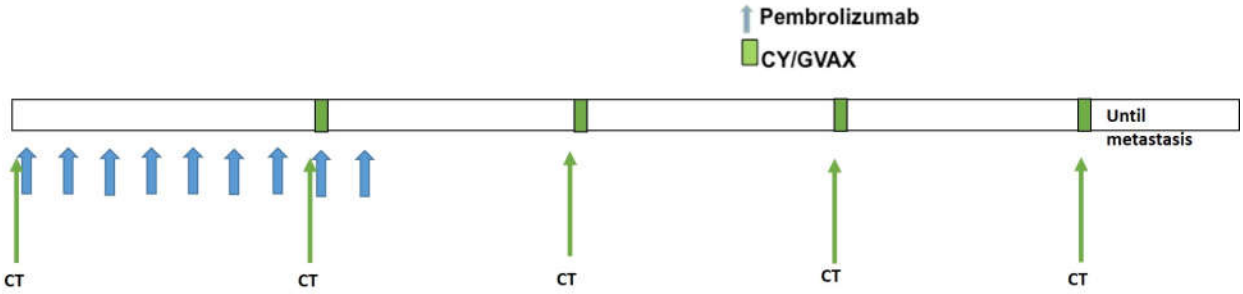
SCHEMA



Extended Treatment Phase (for patients with no evidence of disease or no metastatic disease who opt to stay on trial)



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1. OBJECTIVES

1.1 Primary Objectives

1.1.1 To determine the distant metastasis free survival (DMFS) as evidenced by CT scan, PET scan, or death, in subjects with locally advanced pancreatic cancer (LAPC) who have received standard chemotherapy, who are treated with GM-CSF secreting allogeneic pancreatic cancer vaccine (GVAX) and pembrolizumab prior to, in conjunction with, and after stereotactic body radiation therapy (SBRT).

1.2 Secondary Objectives

1.2.1 To assess the safety of the combination GVAX/pembrolizumab given prior to, in conjunction with, and after SBRT in subjects with LAPC by measuring the number of grade 3 and 4 toxicities according to National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE; Version 4.0) that occur after Cycle 1, Day 1 combination immunotherapy

1.3 Exploratory Objectives

1.3.1 To evaluate the effects of combination of pembrolizumab, GVAX, and SBRT upon the activation and expansion of T effector cells (Teffs) infiltrating into the tumor microenvironment (TME) compared to data from ongoing JHU trials evaluating the TME in patients treated with 1) chemotherapy and SBRT alone, or 2) immunotherapy alone.

1.3.2 To monitor the IHC of immune parameters relevant to and the activation of PD-L1/PD-1 associated immunosuppressive pathways, vaccine-induced immune regulatory signatures, and peripheral and intratumoral antigen specific T cell responses after treatment with pembrolizumab, CY, GVAX, and standard multimodality treatments

1.3.3 To assess tumor tissue for molecular determinants of response, progression and disease stability using next generation sequencing technology.

1.3.4 To assess tumor burden dynamics using both standard protein biomarkers such as CA19-9 and other exploratory circulating biomarkers in serial collections of sera and plasma at baseline and throughout treatment.

1.3.5 To assess the baseline characteristic of the subjects enrolled and to correlate these molecular and clinicopathologic criteria with treatment response and toxicity. DNA will be extracted from whole blood and used to evaluate for any germline mutations which may correlate with response or toxicity.

1.3.5 To collect peripheral blood lymphocytes to explore the association of PD-1 positivity, and lymphocyte activation markers with clinical responses

1.3.6 To determine the overall survival (OS) of subjects with LAPC treated with standard chemotherapy who subsequently receive GVAX/pembrolizumab and SBRT.

1.3.7 To determine the local progression free survival (LPFS) of subjects with LAPC treated with standard chemotherapy who subsequently receive GVAX/pembrolizumab, and SBRT using immune related response criteria

1.3.8 To assess the surgical resectability rate of LAPC in subjects treated with standard chemotherapy who subsequently receive GVAX/pembrolizumab and SBRT.

1.3.9 To assess the pathological response rate of subjects with LAPC treated with standard chemotherapy who subsequently receive GVAX/pembrolizumab and SBRT who become surgically resectable candidates as per NCCN guidelines.

1.3.10 To evaluate the quality of life as per the EORTC QLQ-C30/Pan26 questionnaire of subjects with LAPC treated with standard chemotherapy who subsequently receives GVAX/pembrolizumab, and SBRT.

1.4 Primary Endpoint

1.4.1 DMFS as defined as the duration of time from start of treatment to identification of distant metastases on imaging or death, whichever occurs first.

1.5 Secondary and Exploratory Endpoints

1.5.1 Efficacy endpoints

- OS from the time of cycle 1, day 1 of immunotherapy until death from any cause.
- LPFS from the time of cycle 1, day 1 of immunotherapy until first documented local progression or death
- Surgical resectability after therapy as determined by our pancreatic multidisciplinary group based upon NCCN guidelines for resectability
- Pathologic response as determined by surgical margins and residual disease
- Quality of life as per the EORTC QLQ-C30/Pan26 questionnaire

1.5.2 Safety endpoints

- Number of grade 3 and 4 toxicities according to National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE; Version 4.0) that occur after Cycle 1, day 1
- Incidence, nature and severity of all adverse events that occur on or after Cycle 1, Day 1

1.5.3 Correlative studies endpoints

- IHC, flow cytometry, quantitative PCR assays and microarray analysis compared between of pre- and post-treatment tumor specimens to evaluate
  - Immune parameters relevant to the PD-L1/PD-1 pathway
  - Densities and distribution of T-cells in TME
  - Macrophage markers
  - Expression of T helper cell differentiation markers
- Cytokine/chemokine assays to assess changes in intratumoral inflammatory markers
- Whole exome sequencing to identify neoantigens secondary to radiation therapy by comparing tumor-specific non-synonymous mutations before and after treatment
- Peripheral antigen specific T-cell responses
- Intratumoral antigen specific T-cell responses
- Biomarker marker changes (including standard protein biomarkers such as CA 19-9) and correlation to evaluate for prognostic or predictive factors
- To assess correlation between immune parameters and clinical outcomes using univariate and multivariate Cox regression models

1.6 Study Design

This is a single-center, open label, phase II clinical trial to evaluate the clinical activity of a combination of GVAX with pembrolizumab in patients receiving standard chemotherapy and SBRT for LAPC. We will enroll subjects with LAPC diagnosed based upon criteria from NCCN Guidelines as determined by review of imaging and pathology at our institutional multidisciplinary pancreatic tumor clinic and tumor board. The patients will be evaluated one to five weeks after having received at least four 28-day cycles of FOLFIRINOX based or gemcitabine/abraxane based chemotherapy. Patients should not receive more than 8 cycles of chemotherapy prior to enrollment on study. Patients will be eligible for enrollment if they are free from metastatic disease according to CT, PET, or MRI imaging following chemotherapy.

Within seven weeks of receiving the last dose of chemotherapy, patients will subsequently undergo EUS-guided fiducial placement along with core biopsy of the pancreas tumor and research blood draws to evaluate for circulating tumor cells and other inflammatory markers, as well as an SBRT simulation. Participants will then receive their first dose of combination immunotherapy, consisting of cyclophosphamide (Cy) 200 mg/m^2 given intravenously (IV) and pembrolizumab 200 mg IV on day 1 followed by GVAX, administered as six intradermal injections, on day 2. Three weeks later, subjects will receive their second dose of combined immunotherapy on the same day as initiation of SBRT (6.6 Gy x 5 days).

Three to six weeks after completion of SBRT, patients will undergo repeat imaging with FDG-PET, CT, or MRI to evaluate for metastatic disease, progression, and/or surgical resectability. If participants are deemed a surgical candidate, they will be offered surgical resection or NanoKnife treatment at Johns Hopkins Hospital. If the

patient is found to have an unresectable tumor during surgery, research core biopsies will be obtained intraoperatively. If participants still have locally advanced tumors they will undergo an additional EUS-guided tumor biopsy. Patients who undergo Nanoknife treatment will have the post-treatment biopsy obtained intraoperatively. Both the surgical group and persistent LAPC group will be treated with an additional two cycles of FOLFIRINOX based or gemcitabine/abraxane based therapy. Surgery and chemotherapy are considered standard of care. Patients will be considered off study between 28 days after Cycle 2 of immunotherapy and resuming Cycle 3 of immunotherapy, while they are receiving SOC treatment. If imaging or surgery had shown local progression of disease or poor pathologic response, or if chemotherapy intolerance has developed, patients who had received prior FOLFIRINOX can alternately receive gemcitabine/abraxane and vice versa. At completion of chemotherapy, patients will have eligibility criteria re-confirmed to resume every 3 week cycles of combination immunotherapy for six additional cycles or until development of distant metastases. Participants with metastatic disease to the liver or safely biopsiable other metastases (as determined by our interventional radiology team) after the initial immunotherapy will additionally be offered biopsy of the metastatic lesions. Patients who do not undergo surgery will be on trial for approximately nine months, while those who undergo surgery would be expected to be on trial for approximately eleven months.

If patients who have received surgery develop AEs to pembrolizumab, they will be allowed to continue receiving CY/GVAX to complete the eight total cycles of immunotherapy.

Patients who show no evidence of disease or do not develop metastatic disease at the completion of the eight total cycles of therapy will have the option of continuing on the **Extended Treatment Phase** of every three-week pembrolizumab for an additional nine treatments with concurrent every six-month CY/GVAX for four doses total. Patients who choose to continue in this phase will be on trial approximately 35 months if they go to surgery, and those who do not go to surgery will be on trial approximately 33 months.

All patients will undergo standard of care evaluations consisting of history and physical, CT of the chest/abdomen/pelvis or MRI abd/pelvis and non-contrast CT chest (if do not tolerate contrast) every 3 cycles/months to evaluate for local progression and metastatic disease while they are on study.

The primary endpoint is DMFS, defined as the time from first treatment administration to distant metastasis as evidenced by CT scan, PET scan, or death. Individuals will be censored at the date of last scan if no event has occurred. OS is defined as the time from first treatment administration until death with patients censored at the last follow-up visit. LPFS is defined at the time from first treatment administration to local progression as evidenced by CT scan, PET scan, or death. Additional endpoints including subsequent surgical resectability, QoL evaluations (EORTC QLQ-C30/Pan26 questionnaire), pathologic response, and exploratory objectives (described

above) will be monitored.

2. BACKGROUND

2.1 Disease Type

Over 46,000 people were diagnosed with pancreatic ductal adenocarcinoma (PDAC) in the United States in 2014, with only a 6.7% expected 5 year survival.[1] Surgical resection is the only potentially curative modality of treatment; however, only about 8% of patients are deemed surgical candidates. Of even those who receive treatment, 79% will eventually succumb to recurrent disease.[2] In addition, the vast majorities of patients are considered locally advanced (involving adjacent vessels, nerves, and other structures) or metastatic at diagnosis, and thus nonsurgical. Unfortunately, there is no established standard of care in the United States at this time for treatment of locally advanced pancreatic cancer (LAPC), and its overall mortality is grim.

2.2 Management of Locally Advanced Pancreatic Cancer (LAPC)

Though the treatment for LAPC consists of a combination of radiation therapy (RT) and chemotherapy, optimal treatment sequence, technique, and dosing are controversial. Chemotherapy and RT are mainly effective in LAPC at improving local control and increasing the likelihood of a margin-negative resection (ECOG 4201).[3] Induction chemotherapy followed by chemoradiation result in better outcomes when compared to other treatment sequences.[4] However, conventional external beam radiation therapy (EBRT) can take up to 6 weeks to complete, is given with low dose chemotherapy, delays full-dose chemotherapy, and can lead to high rates of grade 3-4 acute toxicity (ECOG 4201 and FFCD).[3, 5]

Recent advancements in RT delivery techniques have led to increased use of stereotactic body radiation therapy (SBRT) due to its shorter duration (3-5 days), increased feasibility, and established efficacy in other disease sites. Earlier studies evaluating SBRT in patients with LAPC have reported superior local control in comparison with EBRT but resulted in high rates of grade 2-4 late GI toxicity.[6] A prospective multicenter phase II study of SBRT five fractions (5-6.6 Gy/fraction for a total dose of 25-33 Gy) following induction gemcitabine chemotherapy in 49 patients with LAPC was recently reported.[7] The median OS was 13.9 months (95% CO: 10.2-16.7) and metastasis free survival was 7.7 months (95% CI: 5.8-10.2). The median local PFS was not observed and 78% were free from local progression at 1 year. Rates of acute and late grade ≥ 2 gastritis, fistula enteritis, or ulcer toxicities were 2% and 11%. Five fraction SBRT not only provided superior local control but also resulted in a lower toxicity profile than the single fraction SBRT. There was also a significant improvement in pain scores ($p = 0.001$) and no decrease in quality of life. Studies evaluating combination chemotherapy and SBRT are ongoing. However, the addition of immunotherapy may potentially provide further benefit by additionally targeting PDAC with a completely different mechanism of action.

2.3 Vaccine Therapy (GVAX)

Immunotherapy has been investigated as a potential concurrent treatment mechanism by stimulating the immune system to recognize a diverse array of tumor antigens. Vaccine therapy has been successful in stimulating immunologic killing of tumor cells via alternate mechanisms than that of chemotherapy or radiation. The GVAX pancreas vaccine is a combination of two irradiated, granulocyte-macrophage colony-stimulating factor (GM-CSF) secreting allogeneic pancreatic tumor cell lines.[8, 9] GM-CSF is an important cytokine in inducing the growth and differentiation of dendritic cells, which act as antigen-presenting cells in encoding tumor antigens. Autologous GM-CSF secreting vaccines have shown immune activation in 10-40% of treated subjects in melanoma, renal cell, prostate, lung, breast, and pancreatic cancers.[10-12] However, autologous vaccines are often technically difficult to produce, and so allogeneic GM-CSF vaccines have been trialed and shown to be safe, tolerable, and prime even HLA-incompatible CD8+ effector T cells to tumor beds.[9, 13]

The initial Phase I study of GVAX in PDAC was a dose escalation trial of adjuvant vaccination in 14 patients with Stage 2 or 3 disease.[9] Subjects received vaccination 8 weeks following resection, then adjuvant chemoradiation, then three additional monthly vaccinations. Treatment was well tolerated, with toxicities limited to grade 1 and 2 local reactions at the vaccine site, and self-limited systemic rashes, with DTH responses observed in 1 of 3 patients receiving 10^8 and in 2 of 5 patients receiving 5 x 10^8 vaccine cells. Analysis of 60 patients in a follow-up phase II trial of adjuvant GVAX who subsequently received a total of 5 vaccinations in addition to chemoradiation showed 86% one-year survival and 61% two-year survival.[14] The vaccine was again well tolerated, with transient local site reactions, mild eosinophilia, rashes, flu-like symptoms (low grade fever, chills, malaise, arthralgias, myalgias, and fatigue).

Further studies have shown the boosted effect of GVAX by its combination with low dose cyclophosphamide (Cytoxan, CY) as an immune modulator. Tumors have several mechanisms for evading immune surveillance, including the development of tolerance with immunosuppressive regulatory T cells (Treg).[15-18] In murine breast cancer models treatment with CY prior to vaccination showed an enhancing effect with suppression of Treg and increase in effector T cells (Teff).[19] In a phase II trial of treatment for Stage IV pancreatic cancer patients, the combination of CY/GVAX was noted to be safe and well tolerated in gemcitabine resistant metastatic pancreatic cancer, with grade 3/4 treatment related events in only one of 30 subjects.[20] Median survival was 2.3 months versus 4.7 months in subjects receiving GVAX without and with CY, respectively. Pathologic evaluation revealed that there was a trend toward prolonged progression-free survival in subjects who had persistent mesothelin-specific T cell responses with therapy.

An ongoing neoadjuvant trial and adjuvant trial of CY/GVAX in patients with resectable pancreatic cancer (NCT01088789) showed that on pathological examination of PDAC tumor tissue resected just two weeks following a single neoadjuvant dose of

GVAX identified the formation of novel vaccine-induced, immunologically active, tertiary lymphoid aggregates, organized lymph node-like structures, with suppression of Treg pathway, that are not observed in tumor tissue resected from unvaccinated patients.

2.4 anti-PD1/PDL1 blockade (Pembrolizumab (MK-3475 or Keytruda))

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades.[21] Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of $CD8^+$ T-cells and the ratio of $CD8^+$ effector T-cells / $FoxP3^+$ regulatory T-cells seems to correlate with improved prognosis and long-term survival in solid malignancies such as ovarian, colorectal and pancreatic cancer, hepatocellular carcinoma, malignant MEL and RCC. TILs can be expanded *ex vivo* and re-infused, inducing durable objective tumor responses in cancers such as melanoma.[22, 23]

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in various tumors.[24-27] Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues.[24] Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. High expression of PD-L1 on tumor cells (and to a lesser extent of PD-L2) has been found to correlate with poor prognosis and survival in various cancer types, including renal cell carcinoma (RCC),[28] pancreatic carcinoma,[29] hepatocellular carcinoma,[30] ovarian carcinoma.[31] Furthermore, PD-1 has been suggested to regulate tumor-specific T-cell expansion in patients with malignant melanoma.[32] The observed correlation of clinical prognosis with PD-L1 expression in multiple cancers suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab (previously known as SCH 900475) is a potent and highly-selective humanized mAb of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab contains the S228P stabilizing mutation and has no antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) activity. Pembrolizumab strongly enhances T lymphocyte immune responses in cultured blood cells from healthy human donors, cancer patients, and primates. In T- cell activation assays using

human donor blood cells, the EC50 was in the range of 0.1 to 0.3 nM. Pembrolizumab also modulates the level of interleukin-2 (IL-2), tumor necrosis factor alpha (TNFα), interferon gamma (IFNγ), and other cytokines. The antibody potentiates existing immune responses only in the presence of antigen and does not nonspecifically activate T- cells.

The FDA-approved Q2W dose of Pembrolizumab is 2 mg/kg. A fixed dose of 200 mg was, however, recommended by Merck for the Q3W schedule in order to synchronize the schedule of pembrolizumab with GVAX. "200 mg Q3W" is currently being tested in multiple ongoing Merck-sponsored clinical studies including PN012, PN021, PN023, PN024, PN045, PN055, etc. (Investigator's Brochure, Table 19). According to the PN012 study, MK-3475 200 mg Q3W is well tolerated and has a similar toxicity profile as the 2 mg/kg Q2W (Investigator's Brochure, Tables 42-46).

2.5 Preclinical and Clinical Trial Data

Refer to the Investigator's Brochure [IB] for Preclinical and Clinical Data

2.6 Rationale

Attempts to apply anti-CTLA4 and anti-PD1 agents directly to GI tumors and PADC have been limited due to their nonspecific immune modulation and diminished reactivity in these tumor types, except in select populations. For example, though anti-PD1 appears to have minimal activity in patients with colorectal cancer, a subset of colorectal cancer patients with microsatellite instability (MSI) disease, were noted incidentally to have complete response to PD-1 inhibitors.[33] Pathologic review of those more sensitive samples is noted to have increased numbers of neo-antigens (to stimulate immune response) and tumor infiltrating lymphocytes (TILs).[34]

GVAX administration has been shown to activate the tumor microenvironment (TME) by diminishing Tregs and increasing Teffs. This provides an opportunity to convert PDAC TME into an environment similar to that observed in melanomas with infiltrating, but immunosuppressed T cells that may be more amenable to checkpoint inhibitors.

The combination of ipilimumab (CTLA-4 inhibitor) with GVAX in advanced pancreatic cancer patients is ongoing, and has shown promise in a phase I study of 30 patients with previously treated PDAC showing median OS 3.6 v 5.7 months and 7 versus 27% 1-yr OS in patients treated with ipilimumab without and with GVAX respectively.[35] However, anti-CTLA4 antibodies may have higher toxicity profiles than PD-1 inhibitors. Additionally, PD-1 ligand is highly expressed in a variety of human tumors, including some pancreatic cancer and thus may be a more specific target.[36] In addition, treatment of tumors with GVAX in preclinical models demonstrate that the increased Teffs leads to secretion of interferon-ɤ, which subsequently upregulates the PD-1/PD-L1 pathway.[37, 38] The synergistic effect has been demonstrated in a preclinical model of PDAC where the combination of anti-PD-

1 and anti-PD-L1 antibodies with CY/GVAX leads to an enhanced infiltration of effector T cells into PDAC tumors as well as the cure rate in PDAC tumor-bearing mice.[38]

This clinical trial will therefore evaluate the combination of CY/GVAX and anti-PD-1 antibody (pembrolizumab) for LAPC following induction chemotherapy given before and after local therapies including SBRT and possible surgery for those downstaged to the resectable stage.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients with histologically proven, surgically unresectable, locally advanced pancreatic adenocarcinoma (at diagnosis) or with mixed cell type with predominant histology of adenocarcinoma (by NCCN guidelines)

3.1.2 Patients must have received either FOLFIRINOX based or Gemcitabine/Abraxane based chemotherapy for 4-8 cycles with last dose of therapy between 1-5 weeks of study enrollment, with no evidence of metastatic disease
Note:
- 12-24 doses of Gem/Abraxane that must be given over 16-38 weeks
- 8-16 doses of FFX that must be given over 16-38 weeks

3.1.3 Age $\geq$18 years

3.1.4 ECOG performance status 0-1 (**Appendix A**)

3.1.5 Life expectancy greater than 3 months

3.1.6 Adequate hematologic, renal, and liver function as defined below:

White blood cell count	$\geq$ 3,500 cells/mm^3
Absolute neutrophil count	$\geq$ 1,500 cells/mm^3
Hemoglobin	$\geq$ 9g/dL
Platelets	$\geq$ 80K/mm^3
Serum creatinine	$\leq$ 2.0mg/dL
AST and ALT	$\leq$ 3 x ULN
Total bilirubin	$\leq$ 1.5 x ULN*

*Subjects with Gilbert's Syndrome should have direct bilirubin within normal institutional limits

3.1.7 Female patient of childbearing potential (WOCBP) [free from menses for >2 years, post hysterectomy / oophorectomy, or surgically sterilized] must have a

negative urine or serum pregnancy test. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required to be shown as negative for the patient to be eligible.

3.1.8 WOCBP must be willing to use either two adequate barrier methods *or* a barrier method plus a hormonal method of contraception to prevent pregnancy or to abstain from heterosexual activity throughout the study, starting with Visit 1 through 120 days after the last dose of study therapy. Approved contraceptive methods include for example; intrauterine device, diaphragm with spermicide, cervical cap with spermicide, male condoms, female condoms with spermicide, or oral contraceptives. Spermicides alone are not an acceptable method of contraception.

Male patients must agree to use an adequate method of contraception starting with the first dose of study drug through 120 days after the last dose of study therapy.

3.1.9 Must be willing to be treated with SBRT and have surgical resection (if eligible) only at Johns Hopkins Hospital

3.1.10 Patients must be able to have fiducials placed. If not, the tumor must be posterior and adjacent to the aorta and treatment will only be permitted at the discretion of the Principal Investigator.

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

3.2 Exclusion Criteria

3.2.1 Patients who have been off of FOLFIRINOX or gemcitabine/abraxane therapy for more than 49 days prior to treatment on study

3.2.2 Patients who have had more than one line of chemotherapy for LAPC (other than the 4-8 cycles of FOLFIRINOX based or gemcitabine/abraxane based chemotherapy). Patients will be allowed to switch between FOLFIRINOX and Gemcitabine/Abraxane due to intolerance, but cannot have switched chemotherapy regimens due to radiographic or clinical disease progression.

3.2.3 Patients who have only received single agent Gemcitabine chemotherapy. Abraxane component may be reduced or modified but must be included for a minimum of two cycles.

3.2.4 Presence of duodenal or gastric invasion by the tumor as noted by EGD at time of fiducial placement

3.2.5 Patients with a history of prior treatment with immunotherapy agents

(including, but not limited to: IL-2, interferon, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-OX-40, anti-CD40, or anti-CTLA-4 antibodies).

3.2.6 Is currently participating or has participated in a study of an investigational agent or using an investigational device

3.2.7 Patients receiving active immunosuppressive agents or chronic use of systemic corticosteroids within 14 days of vaccine treatment

*Note: **Special considerations for vaccination**: Study-related treatments may be given after short-term steroid use (≤ 4 days) with prior approval by the protocol chair and IND sponsor.

3.2.8 History of any autoimmune disease, including any history of inflammatory bowel disease, including ulcerative colitis and Crohn's Disease, as well as 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 Principal Investigator.

3.2.9 Known history of interstitial lung disease, has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis

3.2.10 Has a pulse oximetry < 92% on room air.

3.2.11 Requires the use of home oxygen.

3.2.12 Has a known history of Human Immunodeficiency Virus (HIV) (HIV1/2 antibodies), hepatitis B, or hepatitis C infection.

3.2.13 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina, cardiac arrhythmia, metastatic cancer, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.14 Patients who have had surgery within 28 days of dosing of investigational agent, excluding minor procedures (dental work, skin biopsy, etc.), celiac plexus block, and biliary stent placement.

3.2.15 Patients who have received any non-oncology live vaccine therapy used for prevention of infectious diseases within 28 days of study treatment. Examples include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid vaccine.

*Note: Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (e.g. Flu-Mist) are live-attenuated vaccines, and are not allowed within 28 days of study treatment.

3.2.16 Patients receiving growth factors including, but not limited to, granulocyte-colony stimulating factor (G-CSF), GM-CSF, erythropoietin, within 14 days of study drug administration. Use of such agents while on study is also prohibited

3.2.17 History of severe hypersensitivity reaction to any monoclonal antibody

3.2.18 Patient has a known or suspected hypersensitivity to GM-CSF, hetastarch, corn, dimethyl sulfoxide, fetal bovine serum, trypsin (porcine origin), yeast or any other component of GVAX pancreas vaccine

3.2.19 Any concurrent malignancy or myeloproliferative disorder whose natural history or treatment has the potential to interfere with safety or efficacy assessment of this study's investigational drug. Patients with a previous non-pancreatic, nonperiampullary malignancy without evidence of disease for > 5 years will be allowed to enter the trial.

3.2.20 Women who are pregnant or breastfeeding.

3.2.21 Women of child bearing potential or sexually active fertile men with partners who are women of child bearing potential who are unwilling or unable to use an acceptable method to avoid pregnancy for the entire study and for up to 120 days after the last dose of investigational product

3.2.22 Patient is unwilling or unable to follow the study schedule for any reason.

3.2.23 Presence of any tissue or organ allograft, regardless of need for immunosuppression, including corneal allograft. Patients with a history of allogeneic hematopoietic stem cell transplant will be excluded.

3.3 Additional inclusion criteria for study continuation and extended treatment phase

Patients must have eligibility checked prior to initiation of Cycle 3 of immunotherapy. Research participants must meet the following criteria for post-operative/post-chemotherapy combination immunotherapy.

3.3.1 ECOG performance status 0-1 (**Appendix A**)

3.3.2 Adequate hematologic, renal, and liver function as defined below:

Absolute neutrophil count ≥ 1,000 cells/mm3
Hemoglobin ≥ 8g/dL

Platelets ≥ 80K/mm3
Serum creatinine ≤ 2.0mg/dL
AST and ALT ≤ 3 x ULN
Total bilirubin ≤ 1.5 x ULN*

*Subjects with Gilbert's Syndrome should have direct bilirubin within normal institutional limits

3.3.3 Female patients of childbearing potential (WOCBP) must have a negative urine or serum pregnancy test. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be require to be shown as negative for the patient to be eligible.

3.3.4 WOCBP must be willing to use either two adequate barrier methods OR a barrier method plus a hormonal method of contraception to prevent pregnancy or to abstain from heterosexual activity throughout the study.

Male patients must agree to use an adequate method of contraception.

Research patients with any of the following will be excluded from study continuation.

3.4 Additional exclusion criteria for study continuation and extended treatment phase

3.4.1 Radiographic evidence of metastatic disease

3.4.2 Patients receiving active immunosuppressive agents or chronic use of systemic corticosteroids within 14 days of vaccine treatment

*Note: **Special considerations for vaccination**: Study-related treatments may be given after short-term steroid use (≤ 4 days) with prior approval by the protocol chair and IND sponsor.

3.4.3 Has pulse oximetry of < 92% on room air, or requires the use of home oxygen

3.4.4 Uncontrolled illness or infection as described in **3.2.13**

3.4.5 Breastfeeding or pregnancy

3.4.6 New diagnosis of cancer other than non-melanoma skin cancer, non-invasive bladder cancer, early stage prostate cancer, or carcinoma in situ of the cervix.

3.4.7 Patients who have had surgery within 28 days of dosing of investigational agent, excluding minor procedures mentioned in **3.2.14**

3.4.8 Patients who have received any non-oncology live vaccine therapy used for prevention of infectious diseases within 28 days of study treatment. Examples

include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid vaccine.

*Note: Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (e.g. Flu-Mist) are live-attenuated vaccines, and are not allowed within 28 days of study treatment.

3.4.9 Patients receiving growth factors including, but not limited to, granulocyte-colony stimulating factor (G-CSF), GM-CSF, erythropoietin, within 14 days of study drug administration. Use of such agents while on study is also prohibited

3.4.10 Patient is a WOCBP or male who is unwilling or unable to use adequate method of birth control to avoid pregnancy for the entire study and up to 120 days after the last dose of investigational product

3.4.11 Patient is currently participating or has participated in a study of an investigational agent or using an investigational device

3.4.12 Patient is unwilling or unable to follow the study schedule or procedures for any reason

3.5 Inclusion of Women and Minorities

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

4. TREATMENT PLAN

4.1 Agent Administration

Treatment will be administered on an outpatient basis. Dosing delays are described in **Section 5.2**. Subjects will receive two initial treatments of combined immunotherapy (pembrolizumab and GVAX) separated by three weeks after completing 4-8 cycles of FOLFIRINOX based or gemcitabine/abraxane based therapy and undergoing pre-screening for metastatic disease. After receiving the first two cycles of combination immunotherapy and SBRT, patients will be reevaluated for surgery. If eligible for surgery, they will undergo traditional surgery or NanoKnife resection at Johns Hopkins Hospital. If they undergo surgery or continue to have LAPC, subjects will be treated with two further cycles of FOLFIRINOX based or gem/abraxane based therapy. Subjects who showed no obvious clinical improvement for persistent LAPC, developed intolerance to their previous chemotherapy regimen, or had no evidence of treatment effect on surgical resection can be offered gemcitabine/abraxane based therapy if they had previously received FOLFIRINOX or vice versa. After completing chemotherapy, subjects will then start on every 3 week cycles of combination immunotherapy for six additional cycles (combined up to eight cycles of combined immunotherapy).

Patients who remain free of metastatic disease at the completion of eight cycles of combined immunotherapy will be eligible to enroll in the optional **Extended Treatment Phase** during which patients will receive every 3 week dosing of pembrolizumab for nine additional doses (total 17 doses) and every 6 month CY/GVAX for an additional four doses (total 12 doses).

Table 1: Study Regimen

Agent	***Premedications, Precautions***	***Dose***	***Route***
Cyclophosphamide	Subjects may be pre-medicated with anti-emetics	200 mg/m2 in 100 mL NS	IV infusion over 30 minutes
GVAX	EMLA cream (approximately 2.5gms/site at least 1 hour prior to vaccination)	$5x10^8$ cells	Six intradermal injections
Pembrolizumab	No prophylactic pre-medications unless indicated by previous experience in an individual subject	200 mg	IV over 30 minutes

Infusion times are approximate (+/- 10 min) and may need to be adjusted based on subject tolerability.

Please see **Section 5.2** for guidance regarding dosing delays.

4.1.1 [redacted]

4.1.2 ***Cy (Cytoxan^{R})*** The single intravenous (IV) dose of 200 mg/m^2 Cy is chosen based on our data showing that this single low IV dose given with a GM-CSF-secreting breast cancer vaccine is equivalent to the repetitive oral metronomic doses of Cy in reducing Treg levels in the PDA TME and facilitating enhanced T cell activation. Cy is a FDA-approved standard chemotherapy agent. Subjects may be pre-medicated prior to administration with anti-emetics per institutional guidelines.

4.1.3 ***Anti-PD-1 Therapeutic Antibody*** **Pembrolizumab** (KEYTRUDA®, MK-3475) is a potent and highly-selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. It is FDA-approved for treating metastatic melanoma. The recommended dose of KEYTRUDA is 2 mg/kg administered as an intravenous infusion over 30 minutes. In this study, pembrolizumab will be administered IV over 30 minutes at 200 mg.

Antiemetic medications should not be routinely administered prior to dosing except as indicated by patient's prior reaction

4.1.4 SBRT and Fiducial placement

Treatment on this protocol requires placement of 1-5 gold (99.9% pure, 1-5 mm length, visicoils, or other) fiducials for targeting purposes. The fiducials will be used as surrogates for targeting the daily tumor position during treatment. The fiducials will be placed directly into the tumor and/or periphery under endoscopic ultrasound or CT guidance. Fiducials may be implanted prior to enrollment as this is an acceptable standard of care procedure for any patient receiving radiotherapy for locally advanced pancreatic or periampullary cancer. Also, if a patient had an attempted surgical resection that was aborted, fiducials may have been implanted intraoperatively, which is also allowable prior to study enrollment.

If fiducials are not placed intraoperatively and/or prior to enrollment, placement will be done and is expected to be done on an outpatient basis. In rare occurrences when fiducials/clips cannot be placed, patients may be treated at the discretion of the PI.

SBRT Simulation (planning)

1) Simulation should be done following placement of fiducials; however, this may vary and is at the discretion of the principal investigator.
2) Typically, patients will be positioned supine in an Alpha Cradle or equivalent immobilization device that will be custom-made for each patient.
3) Standard free-breathing CT and respiratory-correlated 4-D pancreatic protocol CT will be obtained on each patient. The 4D-CT scan will be used for characterizing target motion during quiet respiration. For more accurate tumor delineation, an arterial phase pancreatic protocol CT may be obtained (typically during expiration breath hold, 1.25 mm

slices). Fiducial to fiducial fusions between these scans should be utilized whenever possible. The simulation scan should include T4/T5 to L5/S1 (upper abdomen).

4) IV and oral contrast must be used for simulation, unless the patient has an allergy. In these situations, the plan should be fused with an MRI (ideally in a similar treatment position), or if not able to undergo MRI, premedication with steroids and antihistamines as necessary.
5) Motion management can be addressed using respiratory gating, breath-hold, or respiratory tracking. The goal is to reduce motion from typically 11-22 mm peak to less than 5 mm. If the fiducial motion cannot be decreased to 5 mm or less, then respiratory gating using either the Varian Respiratory Management (RPM) system or the Elekta Active Breathing Coordinator (ABC) will be utilized for treatment delivery. Prior to simulation, standard guidelines will be followed.
6) As long as the specified dosimetric parameters for SBRT are reached, patients may be treated on any IGRT-enabled machine.
7) All patients must start Linac based SBRT within 4 weeks of the simulation scan.
8) A research ultrasound (US) may be conducted at the time of simulation. In order to monitor the abdominal soft tissue motion, the Department of Radiation Oncology has developed a 4D ultrasound technique based on an ultrasound probe holder and a continuous motion monitoring software. The 4D ultrasound image is acquired by using a motorized 3D ultrasound probe and image continuously. 4D ultrasound is a new non-ionizing and non-invasive imaging technique that continuously monitors the tumor motion during the radiation treatment in real time.

SBRT Treatment Planning

1) When available, an FDG-PET scan is preferred for treatment planning purposes.
2) An SBRT treatment plan will be developed using Pinnaclebased on tumor geometry and location. Institutional standards for radiation quality assurance and radiation delivery will be utilized.
3) The tumor volume (GTV), as identified on the treatment planning CT, will be contoured by an attending physician from Johns Hopkins Hospital. The final GTV will be defined by the attending radiation oncologist after reviewing the diagnostic CT, respiratory-correlated 4D-CT scan, pancreas protocol CT, and/or the FDG-PET/CT scan. These scans will be used to define the ITV (internal target volume). The final PTV (planning treatment volume) expansion will consist of an additional 2-3 mm of margin expansion, except if the margin results in expansion into the duodenum or stomach. In these cases, margin expansion is allowed to be non-uniform. The dose will be prescribed to the isodose line that completely surrounds the PTV. It is

recommended that 6-12 co-planar fields or arc fields be used in the radiation treatment plan.

4) Contours of the fiducials used for target localization will be generated on the applicable image sets, to be used for patient setup on treatment.
5) Radiation dose to the adjacent normal tissue will be minimized. Based on an analysis of duodenal toxicity representing pooled data from 3 previous prospective studies, the following dose constraints must be met: V15<9cc, V20<3cc. The duodenum (duo@PTV) as defined for these dosing parameters includes the entire duodenum on the same axial plane as the PTV and duodenum 1 cm above and 1 cm below the PTV. V15 and V20 are defined as the percent volume receiving 15 Gy and 20 Gy, respectively. No more than 1cc of the proximal duodenum or proximal stomach may exceed 33 Gy. The remainder of the normal tissues will be limited as follows:
    - Liver (excluding tumor): 50% should be limited to <12 Gy
    - Kidney: Combined volume for both should have 75% <12 Gy
    - Stomach and duodenum: V15<9cc and V20<3cc. 50% should be limited to <12 Gy (no more than 1 cc of proximal stomach can receive >33 Gy)
    - Spinal Cord: no more than 1cc can receive >8 Gy
6) No more than 1cc of the PTV can receive >130% of the prescription dose (4290cGy for 6.6Gy x 5).
7) Greater than 90% of the PTV should receive 100% of the prescription dose (3300cGy for 6.6Gy x 5; 2500cGy for 5Gyx5).
8) If above constraints cannot be achieved, then 100% of the GTV must receive at least 25 Gy (an allowed minor deviation, which will be documented).
9) When the research 4D ultrasound is used during the simulation, the US probe in the CT will be contoured and we will avoid placing any radiation beams directly through the ultrasound probe.

   If this constraint cannot be met, the patient should be removed from the protocol.

Linac based SBRT Treatment Delivery

Patients will receive 5 fractions of 6.6 Gy delivered over a five-day period, as delineated above. Ideally all 5 fractions should be delivered Monday through Friday; however, treatment may be delivered over 2 weeks, as long as the patient receives at least 2 fractions per week.

Treatment Delivery (LINAC-based):

1) Initial patient positioning will be based on volumetric kV or cone-beam CT imaging with shifts to bony anatomy as appropriate.

2) Orthogonal kV/MV, kV/kV projection, or cbct imaging will be used to verify the location of the fiducials prior to delivery of the first treatment beam. A secondary shift based on the location of fiducials may be utilized, as indicated by the position of the fiducials. For free-breathing treatments, kV fluoroscopic images should be obtained to confirm the anticipated position of these fiducials during the entire respiratory cycle.
3) Active monitoring of treatment delivery accuracy will be accomplished using kV and/or MV projection imaging, either immediately before or during all (or a subset of) treatment fields.
4) Patient-specific dosimetric quality assurance (QA) will be performed as per standard practice in the Department of Radiation Oncology and Molecular Radiation Sciences at Johns Hopkins Hospital.
5) When the research 4D ultrasound is used during the simulation, active 4D ultrasound will be used during the entire treatment, the treatment will not be altered during ultrasound acquisition.

4.2 General Concomitant Medication and Supportive Care Guidelines

4.2.1 Cyclophosphamide (Cy)

Acute reactions will be managed using standard therapy for acute drug reactions as per institutional guidelines

4.2.2 GVAX Pancreas Vaccine

Local skin reactions at vaccine sites may be treated topical lotions (e.g. aloe vera or vitamin E). Pruritus can be managed with topical or systemic benadryl. Significant local inflammation leading to severe pain may be treated with oral analgesics. Local ulceration should be managed with local wound care, with or without antibiotics, and should be evaluated on a case-by-case basis.

4.2.3 Pembrolizumab

Pembrolizumab is a humanized monoclonal Ab. Subjects should be closely monitored for potential adverse reactions during antibody infusion and potential adverse events throughout the study.

Unexpected Grade 3 or greater laboratory abnormalities should be repeated within 24-72 hours if clinically indicated and monitored as necessary to determine if event meets toxicity criteria.

4.2.3.1 Infusion Reactions

Pembrolizumab infusion reactions may consist of fever, chills/rigor, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash,

vomiting, myalgia, dizziness or hypertension. Severe reactions may include acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. Patients should be closely monitored for such reactions. Guidelines for patients who experience an infusion related or allergic reaction during or after infusion with pembrolizumab are shown below.

Table 2: Guidance on Infusion and Hypersensitivity Reactions

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

4.2.3.2 Immune-Related Adverse Events (IRAEs)

Blocking PD-1 function may permit the emergence of auto-reactive T cells and resultant clinical autoimmunity. Rash/pruritus, diarrhea/colitis,

pneumonitis, hepatitis, and hypothyroidism were drug-related, presumptive autoimmune events, now termed IRAEs.

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.

4.3 Prohibited and Restricted Therapies

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

- Any non-study anticancer or immunotherapy agent (investigational or non-investigational)
- Any other investigational agents
- Any other immunotherapy treatment, including, but not limited to: IL-2, interferon, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-OX-40, anti-CD40, or anti-CTLA-4 antibodies
- Systemically active steroids can be used but should be reported to the Principal Investigator and IND Sponsor. Steroid treatment should be completed at least 14 days prior to resuming study-related treatments (See **Section 5.2** for dosing delays for steroids)
- Filgrastim (Neupogen® or G-CSF) or sargramostim (Leukine® or GM-CSF)
- Prophylactic live vaccines (e.g., Td/Tdap, measles, chicken pox) within 28 days prior to or after dosing combination immunotherapy

4.4 Dosing Criteria

Dosing will be delayed for the following laboratory criteria:

- AST, ALT > 3.0 x ULN
- Total bilirubin >1.5 x ULN (patients with diagnosed Gilbert's Syndrome, direct bilirubin should be within normal institutional limits)
- Serum creatinine > 2.0mg/dL
- Hemoglobin < 8 g/dL
- ANC < 1000/uL
- Platelets < 80 x 10^3/uL

4.5 Definition of an Overdose for this Protocol

Overdose of pembrolizumab is defined as:
The patient has taken (accidentally or intentionally) a dose exceeding the dose prescribed in the protocol by 20%. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, pembrolizumab should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse experience(s) is associated with ("results from") the overdose of test drug or vaccine, the adverse experience(s) is reported as a serious adverse experience, even if no other criteria for serious are met.

If a dose of test drug or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse experience must be reported within 24 hours to the Sponsor and Merck Global Safety. Merck Global Safety (GS) contact information can be found in **Section 6.5.1**.

4.6 Contraception, Use in Pregnancy, Use in Nursing

4.6.1 Contraception

The investigational agents may have adverse effects on a fetus *in utero*. Furthermore, it is not known if the investigational agents have transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 2 years will be considered postmenopausal), or 3) amenorrheaic for <2 years without a hysterectomy and oophorectomy and with a documented FSH value in the postmenopausal range, or 4) not heterosexually active for the duration of the study, or 5) heterosexually active and willing to use 2 methods of birth control (which is also required for the female partners of male patients). The 2 birth control methods can be 2 barrier methods *or* a barrier method plus a hormonal method to prevent pregnancy, used throughout the study starting with Visit 1through 120 days after the last dose of study medication. Male patients enrolled in this study must also agree to use an adequate method of contraception starting with Visit 1 through 120 days after the last dose of study drug.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including

oral, subcutaneous, intrauterine, or intramuscular agents).

Patients should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study. If there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

4.6.2 Use in Pregnancy

The investigational agents may have adverse effects on a fetus; therefore, women with a positive pregnancy test at screening will not be eligible for enrollment. If a patient inadvertently becomes pregnant while on treatment with combination immunotherapy, the patient will immediately be removed from the study. The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor and to Merck Global Safety without delay. The outcome must be reported to the Sponsor within 24 hours and to Merck Global Safety if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). If a male patient's partner becomes pregnant on study the pregnancy must be reported to the Sponsor and to Merck Global Safety as described in **Section 6.5.1**. The study Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor and to Merck Global Safety.

4.6.3 Use in Nursing Women

It is unknown whether the investigational agents are excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, patients who are breast-feeding are not eligible for enrollment.

4.7 Unacceptable Toxicities

Unacceptable toxicities are defined as:

- Treatment-related ≥ grade 4 AEs, or
- Treatment-related grade 3 AEs that do not improve to ≤ grade 2 under therapy within 2 weeks.
- ≥ 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

Exceptions include:

- Alopecia
- Asymptomatic amylase/lipase elevation

Unexpected Grade 3 or greater laboratory abnormalities should be repeated within 24-72 hours if clinically indicated and monitored as necessary to determine if event meets toxicity criteria.

The proportion of unacceptable toxicities will be monitored. If the toxicity levels are unacceptable (high probability that it is >45% of subjects), then enrollment will be suspended until further review and consideration by the IND Sponsor and MEC.

The proportion of treated subjects with unacceptable toxicity will be monitored using a Bayesian stopping guideline. Subjects will initially be staggered until 6 subjects have been treated and followed for 4 weeks after the completion of SBRT, which translates to 7.5-8 weeks after the start of treatment and includes 2 cycles of GVAX/pembro plus 5 days of SBRT. A Beta (2, 5) prior, representing a toxicity rate of 29%, a slightly conservative estimate, was used in the development of our guidelines. The therapy will be re-evaluated if the posterior probability that the toxicity rate exceeds the 45% boundary is greater than 50%. Once the initial cohort of 6 subjects has been recruited and followed for at least four weeks after the completion of SBRT, toxicity will be monitored continuously. If 4 or more subjects experience unacceptable toxicities during the toxicity assessment period in the first 6 subjects, accrual will be suspended until the toxicity levels have been determined to be acceptable. Then, the remaining participants will be enrolled and monitored routinely. **Table 3** summarizes the stopping boundaries for unacceptable toxicities.

Table 3: The number of toxicities needed to trigger stopping guidelines throughout the course of the study

Number of Subjects	Number of toxicities needed to trigger re-evaluation
6	4
7-8	5
9-10	6
11-12	7
13-15	8
16-17	9
18—19	10
20-21	11
22-24	12
25-26	13
27-28	14
29-30	15
31-32	16
33-35	17

Number of Subjects	Number of toxicities needed to trigger re-evaluation
36-37	18
38-39	19
40-41	20
42-44	21
45-46	22
47-48	23
49-50	24
51-52	25
53-54	26

The probability of triggering the stopping guidelines was assessed for a range of possible true toxicity rates using simulations with 5000 replicates (**Table 4**). The probability of stopping to re-evaluate was 2.6% if the true proportion with an unacceptable toxicity was 25%, the expected value. In comparison, the probability of stopping early is 58.4% and 82.1% if the true proportion with an unacceptable toxicity was 45% or 50%, respectively.

Table 4: Probability of triggering a re-evaluation based upon the proportion with an unacceptable toxicity for a range of true toxicity probabilities

True probability of unacceptable toxicity	Probability of triggering stopping guidelines
10%	0.1%
15%	0.8%
20%	2.3%
25%	6.3%
30%	14%
35%	27%
40%	46%
45%	67%
50%	86%
60%	99%

4.8 Duration of Therapy

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.

A subject must be discontinued from treatment (but may continue to be monitored in the post-treatment follow-up portion of the trial) for any of the following reasons:

- Development of distant metastatic disease (see below)
- The subject or legal representative (such as a parent or legal guardian) withdraws consent for treatment
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s) (see **Section 4.7**),
- Need for >2 dose delays due to the same toxicity as per the dose delay guidelines (see **Section 5.2**). However, if patients have undergone surgery and develop irAEs to pembrolizumab, they will be offered continuation of CY/GVAX monotherapy to complete 8 cycles.
- If in the opinion of the Investigator, a change or temporal or permanent discontinuation of therapy would be in the best interest of the patient. The Sponsor and Merck should be included in this decision,
- Noncompliance with trial treatment or procedure requirements,

- Patient is lost to follow-up
- Patient becomes pregnant.

4.9 Off Study Treatment/Safety Follow-up Visit

Patients are considered off study treatment beginning 90 days after the last immunotherapy. Follow-up visits will be scheduled at the discretion of the patient's local oncologist and the results sent to us if the patient agrees. All attempts will be made to obtain disease-free and overall survival data on each patient.

After a patient is determined to have metastatic disease and is discontinued from combination immunotherapy, a mandatory Off Study Treatment/Safety Follow-Up Visit should be performed approximately 30 days after the last infusion of study medication (or within 7 days prior to initiation of a new anti-cancer treatment, whichever comes first). Procedures and assessments performed at this visit and beyond should follow the respective guidelines as appropriate. The patient will be monitored for adverse events up to the mandatory Off Study Treatment/Safety Follow-Up Visit or to resolution of toxicity to Grade 0-1, whichever occurs later. SAEs that occur within 90 days of the end of treatment or before initiation of a new antineoplastic treatment should also be followed and recorded.

4.10 Duration of Follow Up

Subjects who discontinue from treatment should remain on study and be contacted every 12 weeks (and at 90 days [+14 days] from the EOT) to monitor OS until death, withdrawal of consent, or study closure. Information of other cancer therapies after discontinuation from the study treatment will be collected.

All subjects who discontinued study treatment should continue to be monitored for disease status by radiologic imaging. Disease monitoring should continue to be assessed every 12 weeks until, 1) start of a new antineoplastic therapy (information of the new cancer therapy will be collected), 2) until death, 3) withdrawal of consent, or 4) study closure, whichever occurs first. Patients who complete 2 years of follow up (designated by date of last study treatment) should continue to have their disease status monitored by radiologic imaging every 24 weeks (+/- 30 days), or at the discretion of treating oncologist.

Subjects who are discontinued from the study treatment due to an unacceptable drug-related AE will be monitored for safety until the resolution of the AE to ≤ grade 1 or stabilization or until initiation of a new therapy for their cancer, whichever occurs first.

All subjects will be followed for at least 4 weeks after their last dose of study drug for the development of AEs. SAEs that occur within 90 days of the EOT or before initiation of a new antineoplastic treatment should also be followed and recorded.

Per the FDA requirement, all research patients treated with genetically modified products (pancreatic tumor vaccine) will be followed annually (+/- 2 months) for 2 years per protocol either at Johns Hopkins or until study termination.

If consent is granted, patients at Johns Hopkins who chose to enroll will be followed for disease progression, survival and potential long term toxicity of gene therapy in an existing protocol entitled "Long term follow-up of patients who received lethally irradiated allogeneic pancreatic tumor cells transfected with the GM-CSF gene (IRB # 02-10-14-03, SKCCC J0248)". Consent for this long-term follow up protocol may be obtained at any point during treatment on this protocol.

4.10.1 Continuation of Therapy (Vaccine Boost)

After participants have completed the study, they may be eligible to receive the same pancreatic cancer vaccine through participation in a vaccine boosting protocol entitled "A safety and feasibility trial of boost vaccinations of a lethally irradiated, allogeneic pancreatic tumor cell vaccine transfected with the GM-CSF gene given alone or in combination with either a single intravenous dose or daily metronomic oral doses (IRB# NA_00031401, SKCCC J09100)."

4.11 Criteria for Removal from Study Treatment

Patients will be removed from study treatment when any of the criteria listed in **Section 4.8** applies. The reason for study treatment removal and the date the patient was removed must be documented in the Case Report Form.

4.11.1 Development of Distant Metastases as determined by imaging or laboratory parameters, will be considered to have reached primary outcome.

4.11.2 Pembrolizumab related IRAEs

Permanent discontinuation of pembrolizumab should be considered for any of the following:

1. Severe or life-threatening related adverse reactions, including, but not limited to, any of the following (Sponsor and Merck must be notified in the event of these AEs, and final decision regarding treatment will be made after a discussion):

    - Grade 3-4 toxicity (non-hematologic or hematologic). Grade 3 toxicities may be able to be re-dosed on a case by case basis after approval of the Sponsor and Merck.

    - Diarrhea with abdominal pain, fever, ileus, or peritoneal signs; increase in stool frequency (7 or more over baseline), stool incontinence, need for intravenous hydration for more than 24 hours, gastrointestinal hemorrhage, and gastrointestinal perforation

- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >5 times upper limit of normal
- Total serum bilirubin >3 times upper limit of normal
- Steven-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration or necrotic, bullous or hemorrhagic manifestations
- Severe (i.e., CTCAE Grade 3 or 4) motor or sensory neuropathy
- Any grade Guillain-Barré syndrome, or myasthenia gravis or other neurologic symptoms that impact activity of daily living
- Severe immune-mediated reactions involving any other organs (e.g., nephritis, pneumonitis, pancreatitis, non-infectious myocarditis)
- Immune-mediated ocular disease that is unresponsive to topical immunosuppressive therapy
- Grade 4 infusion reaction

2. Inability to reduce corticosteroid dose for immune-related adverse reactions to ≤10 mg prednisone or equivalent per day

   If any of the above events occur, the investigator should discuss with Sponsor and Merck to make a decision on discontinuation of pembrolizumab study treatment.

In case toxicity does not resolve or improve to ≤ Grade 1 within 12 weeks after last administration of pembrolizumab study drug, study therapy discontinuation should be considered after discussion with the Sponsor and Merck. With Sponsor and Merck agreement, patients still at Grade 2 may continue in the study only if asymptomatic and controlled. Two dosing delays due to the same toxicity will be permitted. In the event of a third occurrence of the same toxicity which would require dosing delay, study therapy will be discontinued permanently, except in select cases of pembrolizumab-only irAEs, at which time post-surgical resection patients may be eligible for CY/GVAX therapy to complete 8 cycles of immunotherapy.

5. DOSING DELAYS/DOSE MODIFICATIONS

5.1 Dose Modifications

Dose reduction or dose increase of CY, GVAX, and pembrolizumab will not be permitted in individual patients.

5.2 Dosing Delays

5.2.1 All scheduled cycles within a course are to be given approximately 3 weeks apart. If necessary, a cycle may be delayed for up to 1 week. In this case, subsequent cycles should continue so that a subject can still receive all cycles given that the cycles are a minimum of 3 weeks apart and they have not experienced an AE necessitating discontinuation. If delayed more than 1 week, the Principal Investigator must be contacted for further instructions on continued treatment. Additional delays or modifications to the treatment schedule must be approved by the Principal Investigator or IND Sponsor.

Pembrolizumab will be withheld for drug-related Grade 4 hematologic toxicities, non-hematological toxicity ≥ Grade 3 including laboratory abnormalities, and severe or life-threatening AEs as per **Table 5**.

Table 5: Pembrolizumab Dose Delay and Discontinuation Criteria

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	

Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:

For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

In case toxicity does not resolve to Grade 0-1 within 12 weeks after last infusion, trial treatment should be discontinued after consultation with the Sponsor. With Sponsor and Merck agreement, subjects with a laboratory adverse event still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled.

If a delay occurs between day 1 and 2 of a cycle:

- Pembrolizumab-related infusion reactions must resolve to baseline prior to administration of GVAX.
- Day 2 GVAX treatment and assessments can be resumed without repeating Day 1 study treatments (Cy and pembrolizumab) if the delay is within 72 hours.
- If the delay is longer than 72 hours, repeat Day 1 and Day 2 study treatments/assessments with a minimum of 2 weeks from the previous Day 1 treatment. This includes steroid treatment requiring at least a 14 day washout prior to resuming study-related treatments.

Systemically active steroids can be used but should be reported to the protocol chair and/or IND sponsor. Extended steroid treatment (> 4 days) must be completed at least 14 days prior to resuming study-related treatments. Study-related treatments may resume after short-term steroid use (≤ 4 days) with prior approval by the protocol chair and/or IND sponsor.

Subjects who have completed surgery that are required to stop treatment with pembrolizumab due to toxicity may stay on study and receive CY/GVAX pancreas vaccine to complete the six-adjuvant (8 total treatments) once pembrolizumab-related toxicity(s) has resolved to a grade 1.

6. ADVERSE EVENTS: LIST AND 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.

The PI has the primary responsibility for continuous internal monitoring for safety, protocol compliance, and identification, grading, coding, and required reporting of all anticipated and unanticipated adverse events and protocol problems. Although this responsibility is usually shared among the PI, research nurse, and data manager, the PI is ultimately responsible for grading and attribution of all events.

All adverse events experienced by subjects will be collected and reported from the first dose of the investigational agent, throughout the study, and will only be followed for 30 days unless related to the investigational agent. All Serious Adverse Events (SAEs) will be collected for 90 days after the end of treatment or until a new antineoplastic treatment is initiated, whichever occurs first.

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.

Patients who experience a Grade 2 or higher irAE should be discussed with the IND Sponsor. In addition, irAEs listed in **Section 6.1.3** must be reported as an Event of Clinical Interest (ECI) within 24 hours to the Sponsor and to Merck Global Safety even if no Serious Adverse Event Criteria are met.

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.

6.1 Definitions

6.1.1 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 not be recorded. Additionally, expected progression of the disease being studied will not be recorded as an adverse event. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy.

6.1.2 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) > 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.)
- Is a new cancer (that is not a condition of the study)
- Is associated with an overdose

Events **not** considered to be serious adverse events are hospitalizations for the:

- Admissions as per protocol for a planned medical/surgical procedure or to facilitate a 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).

6.1.3 Adverse Events of Clinical Interest (ECI) for pembrolizumab

These selected non-serious related adverse experiences are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event of Clinical Interest Case Report Form found in **Appendix B**. Events of clinical interest for this trial include:

- An overdose of Merck's product, as defined in **Section 4.5**, that is not associated with clinical symptoms or abnormal laboratory results.
- An elevated AST or ALT lab value that ≥ 3x the upper limit of normal and an elevated total bilirubin lab value that is ≥ 2x the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is ≤ 2x the upper limit

of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

6.2 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.

6.3 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.

6.4 Handling of Expedited Safety Reports

In accordance with local regulations, the Sponsor will notify investigators of all SAEs that are unexpected (i.e. not previously described in the Investigator Brochure), and definitely, probably, or possibly related to pembrolizumab or CY/GVAX. This notification will be in the form of an expedited safety report (ESR) that is to be faxed to the investigators and the study coordinators 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. The investigator and IRB will determine if the informed consent requires revision. The investigator should also comply with the IRB 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.

6.5 Reporting

6.5.1 General

All adverse events (both expected and unexpected) will be captured on the

appropriate study-specific case report forms (CRFs), with the exception of unrelated adverse events that occur during the off study period between cycles 2 and 3 of immunotherapy (28 days after Cycle 2 of immunotherapy and first dose of study treatment in Cycle 3).

In addition, all serious adverse events, regardless of causality to study drug, will be reported promptly to the IND Sponsor ([redacted]) and Merck's Global Safety ("Merck GS") group within 24 hours of recognition, with the exception of unrelated SAEs that occur during the off study period between cycles 2 and 3 of immunotherapy (28 days after Cycle 2 of immunotherapy and first dose of study treatment in Cycle 3). Serious adverse events should be reported using the form found in **Appendix C**. If this falls on a weekend or holiday, an email notification is acceptable but must be followed by an SAE reporting form on the next business day.

Non-serious Events of Interest will be forwarded to Merck GS and will be handled in the same manner as SAEs.

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner who has provided written consent to provide information regarding pregnancy, that occurs during the trial or within 120 days of completing the trial. All subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported to Merck GS.

[redacted].

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

All serious adverse events will be reported to the IRB and IBC per institutional guidelines. Upon receipt of the report of the serious adverse event by IRB and IBC, follow-up information will be given to the IRB and IBC within 15 days.

6.5.3 Food and Drug Administration (FDA)

All reporting to the FDA will be completed by the sponsor.

6.5.3.1 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.

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.

6.5.3.2 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-Investigator.

6.5.4 Recombinant DNA Advisory Committee (RAC)

Unexpected SAEs believed to be 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. SAEs that are unrelated or related and expected with the investigational product (s) will be reported to RAC in the Annual Report. Follow-up information will be submitted to the RAC as soon as relevant information is available.

7. PHARMACEUTICALINFORMATION

7.1 Cyclophosphamide (Cytoxan®, CY)

7.1.1 Agent Accountability

The IND Sponsor or the Sponsor's representative shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations

7.1.2 Mode of Action

CY is a synthetic antineoplastic drug chemically related to the nitrogen mustards. CY 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.

7.1.3 Description

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

7.1.4 Packaging and Labeling Information

CY is commercially available.

7.1.5 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

CY may be prepared for parenteral use by infusion using any of the following methods:

1. CY constituted with 0.9% sterile sodium chloride may be infused without further dilution.
2. CY 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)

7.1.6 Storage

Store vials at or below 77° F (25° C).

7.1.7 Stability

CY (prepared for either direct injection or infusion) is chemically and physically stable for 24 hours at room temperature or for 6 days in the refrigerator; it does not contain any antimicrobial preservative and thus care must be taken to assure the sterility of prepared solutions.

7.1.8 Route of Administration

CY is administered by IV injection over 30 minutes.

7.1.9 Subject Care Implications

During treatment, the subject'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 CY 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 CY even though CY has been used successfully concurrently with other drugs, including other cytotoxic drugs. CY treatment, which causes a marked and persistent inhibition of cholinesterase activity, potentiates the effect of succinylcholine chloride. If a subject has been treated with CY within 10 days of general anesthesia, the anesthesiologist should be alerted.

CY may interfere with normal wound healing.

7.1.10 Returns and Reconciliation

N/A

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.3 Pembrolizumab

7.3.1 Agent Accountability

The sponsor/investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

7.3.2 Mode of Action

Pembrolizumab is a highly selective humanized monoclonal antibody designed to block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is an IgG4/kappa isotype with a stabilizing sequence alteration in the Fc region.

7.3.3 Description

Clinical Supplies will be provided by Merck as summarized below:

Product Name & Potency	Dosage Form
Pembrolizumab 50 mg	Lyophilized Powder for Injection
MK-3475 100 mg/4 mL	Solution for infusion

7.3.4 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements. Open label kits will be provided for patient dosing.

7.3.5 Preparation

Refer to Procedures Manual for preparation instructions.

7.3.6 Storage

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. Receipt and dispensing of trial medication must be recorded by an authorized person.

Refer to Procedures Manual for Storage conditions.
Clinical supplies may not be used for any purpose other than that stated in the protocol.

7.3.7 Stability

Refer to Procedures Manual for Stability information.

7.3.8 Route of Administration

The reconstituted product is intended for IV administration.

7.3.9 Patient Care Implications

Based on results from the nonclinical studies, there are currently no specific safety considerations. Pembrolizumab is a humanized monoclonal Ab. Thus far, serious infusion reactions have been infrequent and manageable. However, subjects should be closely monitored for potential adverse reactions during antibody infusion and potential adverse events throughout the study. In the event that a subject experiences an allergic reaction to pembrolizumab, treatment (i.e., vasopressors, H2-blockers, antihistamines, H1-blockers, steroids) should be administered, as appropriate, and prophylaxis should be considered. Surveillance for the appearance of HAH is included in all protocols.

Pembrolizumab has the same mechanism of action as BMS 936558. Preclinical studies have suggested similar potency, and PK modeling has suggested similar human PK. Accordingly, the adverse events observed with BMS 936558 may serve as in indicator for the adverse events to expect for Pembrolizumab in cancer patients. Immune-related AEs (irAEs) are of special interest because of the mechanism of action of anti-PD-1 and prior experience with anti–CTLA-4 mAbs. Up to the cut-off date for this IB, the only possibly irAEs included pneumonitis (Grade 2), arthralgia and myalgia. One case of intestinal perforation was not considered immune related.

Overall, pembrolizumab has been safe and well tolerated. However, prompt identification of irAEs and appropriate treatment (e.g. withdrawal of study medication and treatment with corticosteroids) will be critical to optimizing the therapeutic index. Individual protocols outline specific guidance for prompt identification and treatment of irAEs. Timely discussions of how to manage irAEs is also encouraged.

7.3.10 Agent Ordering

Requests for pembrolizumab should be sent via email to:

[redacted]

7.3.11 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to, and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

8. CORRELATIVE/SPECIAL STUDIES

Sample collection, storage, and shipment instructions will be provided in the Procedures Manual.

8.1 Tumor Tissue Studies

4-6 core tumor biopsies will be collected during scheduled endoscopy with fiducial placement. Additional biopsies will be performed after completion of 2 doses of combined immunotherapy and SBRT via research endoscopic biopsy, surgical resection/NanoKnife specimen, or biopsy (for metastases). Post-treatment biopsies will only be obtained if the tumor is thought to be reasonably safe to biopsy, and biopsies not obtained due to concerns for patient safety will not be considered deviations. Additional optional biopsies may be obtained later in the course of therapy. Archival tumor samples may also be collected for every patient (slides and/or blocks). Archival tumor samples will not be collected if the biopsy was a fine needle aspiration. Detailed instructions for tissue collection, processing and shipment are provided in the procedures manual. These tissue samples will be banked for the evaluation of PD-L1/PD-1, their associated immune suppressive pathways and other immune activation pathways to assess the effect of treatment upon the tumor microenvironment and the correlations between these immune parameters and clinical response. Immunohistochemistry, flow cytometry, quantitative PCR assays and microarray

analysis will be employed. In addition, to identify potential neoantigens as a result of radiation therapy, the banked tumor tissues will be used for whole exome sequencing (WES) to identify tumor-specific non-synonymous mutations. Peripheral Blood Lymphocytes (PBL) and tumor infiltrating lymphocytes (TIL), either directly from FFPE tumor sections, or following isolation, will be used for the TCR repertoire analysis by next-generation sequencing.

Archived (previously collected) tumor samples and tissue collected for standard of care may be requested to assess tumor characteristics and the immune system. Tissue, fluid, or blood samples that are collected to detect or treat side effects that are thought to be caused by the immune system may also be collected by the study team. The study team may request optional biopsies to learn more about response or any potential toxicities.

8.2 Peripheral Blood Lymphocytes (PBLs) and Circulating Tumor Cells (CTC)

Post-treatment expression of PD-1 and other lymphocyte activation markers will be measured and correlated with OS and DMFS. PBL will be collected at baseline, surgical evaluation, Cycle 3, and with each subsequent CT scan. PBL are isolated and stored frozen until use. PBL will be banked for measuring peripheral mesothelin-specific T cell responses as an established parameter of immune response to treatment with GVAX. PBL will also be banked for an ELISPOT-based approach similar to the approach we used to define the mesothelin T cell epitopes to validate mutant neoepitopes predicted for HLA-A1 and HLA-A2, including the HLA-A2-binding neoepitopes for the common Kras exon 12 mutations (KrasG12V and G12D). Of the blood collected for peripheral blood analysis, up to 20 cc of blood may be used for isolating circulating tumor cells and/or circulating tumor DNA, respectively. Whole blood of up to 120 cc will be used for PBL processing. During the Post-Immunotherapy Evaluation visit (3-6 weeks post SBRT), approx. 50 cc of whole blood will be aliquoted and processed to plasma to support the isolation of tumor infiltrating lymphocytes. Detailed instructions for blood collection, processing, and shipment are provided in the Laboratory Manual.

8.3 Serum and Plasma Marker Studies

Sera and plasma will be collected at baseline, surgical evaluation, Cycle 3, and with each subsequent CT scan to identify potential therapeutic targets, biomarkers, and predictors of response and autoimmune toxicity through proteomic approaches. Whole blood will be collected in one 5 milliliter Serum Separator Tubes (SST tube) at the designated time points and processed using standard laboratory procedures. Using a pipette, aliquots of 1 mL of serum should be transferred to cryogenic vials and stored at -80oC.

We will also collect whole blood in two 10 mL plasma preparation tube with EDTA (PPT, BD Vacutainer, Franklin Lakes, NJ) and gently swirl tubes to mix blood with

EDTA. Within two hours of collection, the sample will be processed using standard procedures for plasma separation. Plasma will be divided into 1 mL aliquots and stored at -80oC. Detailed instructions for blood collection, processing, and shipment are provided in the Laboratory Manual.

8.4 Diagnostic Tissue Samples

Tissue, fluid, or blood may be collected from standard of care procedures used to treat or diagnose immune related toxicities. Detailed instructions for tissue collection and shipment are provided in the procedures manual.

8.5 Genomic Analysis

Genomic sequencing library construction, whole genome/exome sequencing, whole transcriptome sequencing, microbial sequencing, neoepitope prediction, mutation burden, and bioinformatic analysis will be performed either at an on-campus laboratory or at an off-campus sequencing service. All the samples will be de-identified before sending to any laboratory for sequencing. The FASTQ files, BAM files and VCF files will be generated and analyzed.

Results from the sequencing studies will not be released to the patients. These studies are for research purposes only and are not using a clinically validated platform.

9. STUDY SCHEDULE

Subjects will be evaluated after completing 4-8 cycles of FOLFIRINOX based or gemcitabine/abraxane based chemotherapy for LAPC. They should have a baseline evaluation screening during chemotherapy, and then evaluation for eligibility 14-35 days after last dose of chemotherapy.

Procedure	Screening/Baseline Procedures and Enrollment (within 1-5 weeks of last dose of chemotherapy[1]	Pre-Immunotherapy (2-7 weeks after last dose of SOC chemo)	Cycle 1 Immuno[2] (Up to 7 weeks from last dose of chemotherapy)		Cycle 2 Immuno and SBRT x 5 days (3 weeks after Immunotherapy 1)		Post Immuno Evaluation (3-6 weeks after SBRT)
			C1D1	C1D2	C2D1	C2D2	
Visit Window[3]			-	-	+7	-	+7
Cyclophosphamide			X		X		
GVAX				X		X	
Pembrolizumab			X		X		
Inclusion/exclusion criteria	X						
Demographics	X						
Medical History[4]	X						
Medications	X		X		X		X
Physical Exam[5]	X		X		X		X
Vital Signs and pulse ox[6]	X		X		X		X
Height	X						
Weight	X		X		X		X
Performance Status	X		X		X		X
Hematology profile[7,8]	X		X		X		X
Chemistry profile[7, 9]	X		X		X		X
TSH [7, 10]			X		X		X
Serum/Urine Preg[11]	X		X		X		
CEA[7]	X		X		X		X
CA 19-9[7]	X		X		X		X
Urinalysis and microscopic exam[7, 12]	X						
INR[7]	X						
HLA-Typing (HLA I)			X				
Adverse event evaluation					X		X
Vaccine Site Assessment					X		X
PET-CT, CT, or MRI[13]	X						X
Pathology Review	X						X
PBMC (up to 120cc)[14, 28]			X				X
Serum (up to 5cc)[14, 28]			X				X
Plasma (up to 20cc)[14, 28]			X				X
EUS Core Biopsy[15, 28]	X						X[16, 28]
EUS Fiducial Placement	X						
Simulation Scan[17]		X					
QoL Questionnaire	X				X		X
SBRT x 5 days					X		
Surgical Evaluation							X

[1] While participants are concurrently receiving 4-8 (28-day) cycles of FOLFIRINOX or gemcitabine/abraxane based chemotherapy
[2] Each immunotherapy consists of a combination of CY, GVAX, and pembrolizumab
[3] Longer delays to be approved by the PI and/or sponsor
[4] Includes history of lung disease, HIV, hepatitis B or C infection, and complete cancer history, including primary site of cancer, gross location of primary tumor, histology, histologic grade, date of initial diagnosis, prior cancer therapy regimens
[5] Complete physical exam will be completed at baseline; focused physical examinations will be conducted thereafter. Exams, concomitant medication, AE assessments can be made up to 3 days prior to infusion.
[6] Temperature, respiration rate, blood pressure, pulse oximetry, and pulse should be taken at baseline, after Cyclophosphamide infusion, prior to MK-3475 infusion, and at the end of the infusion.
[7] Labs may be collected within a window of up to 3 days prior to dosing. Unexpected Grade 3 or greater laboratory abnormalities should be repeated within 24-72 hours if clinically indicated and monitored as necessary to determine if event meets toxicity criteria
[8] CBC with differential including absolute eosinophil count, absolute neutrophils, absolute lymphocytes, and platelets
[9] Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
[10] T3 and FT4 to be checked reflexively if TSH is abnormal
[11] For WOCBP. Pregnancy tests must be done within 7 days of the first treatment and then will be repeated with each subsequent therapy (collected within a window of up to 3 days prior to dosing).
[12] Bilirubin, blood, glucose, ketones, leukocytes, nitrite, pH, color, protein, RBC and WBC count, and specific gravity
[13] FDG-PET-CT is preferred for baseline evaluation for SBRT planning. Radiologic evaluations (CT pancreas protocol, Chest, abdomen, and pelvis with contrast) and tumor measurements will be performed at baseline, and then 3-6 weeks after initiating SBRT. Noncontrast CT Chest and MRI Abdomen/pelvis will be done for those with contrast allergies.
[14] See section on correlative studies and lab manual for complete instructions
[15] Endoscopy will be scheduled for concurrent fiducial placement and obtaining 4-6 core biopsies at baseline for archival tissue collection. Archival tissue from non-study biopsies may be collected at any time throughout the study.
[16] EUS Guided biopsy will be obtained for research purposes and archival tissue collection if subject still has LAPC. If subject is a surgical or NanoKnife candidate, biopsy will be obtained intraoperatively during surgical resection. If metastases are noted, subjects will be offered a biopsy of metastases for research purposes.
[17] CT based simulation scan (MRI for those with contrast allergies; premedication for steroids and antihistamines will be allowed for those unable to undergo MRI). May be performed during Cycle 1.

In order to minimize the need for research-only in-person visits, telemedicine visits may be substituted for in-person clinical trial visits or portions of clinical trial visits where determined to be appropriate and where determined by the investigator not to increase the participants risks. Prior to initiating telemedicine for study visits the study team will explain to the participant, what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. Telemedicine acknowledgement will be obtained in accordance with the Guidance for Use of Telemedicine in Research. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions.

After completing two cycles of combination immunotherapy and SBRT, subjects will be evaluated for surgical resectability at multidisciplinary tumor board (based upon clinical health status and resectability as per NCCN guidelines) and presence of distant metastatic disease

- If subjects are deemed to have developed resectable tumors, they will undergo traditional or NanoKnife intervention. If the patient will undergo NanoKnife treatment, the post-treatment biopsy will be obtained intraoperatively.*
  *Note: Surgery date should be determined and posted within 14 days after post-immunotherapy/SBRT evaluation

- If subjects are deemed to still have LAPC, they will have a repeat endoscopic core biopsy of the remaining tumor.

- If a subject is noted to have developed metastases to the liver or other safely biopsiable metastases, they will be offered biopsy of the metastases.

Subjects without metastatic disease will then receive two further cycles of FOLFIRINOX based or gemcitabine/abraxane based chemotherapy either:

- Within 14 days after post-immunotherapy/SBRT evaluation for LAPC

- Within 4-10 weeks postoperatively for subjects who undergo surgical resection

Subjects who up to this point had shown evidence of local progression of disease, developed intolerance to their previous chemotherapy regimen, or showed minimal pathologic response who had previously received FOLFIRINOX will be then eligible for gemcitabine/abraxane for two cycles, and vice versa.

After chemotherapy completion, subjects will then undergo repeat examination and re-screening for eligibility to receive further immunotherapy as per the below schedule:

Procedure	Post-chemotherapy evaluation (2-3 weeks after last dose of SOC chemotherapy)	Combination immunotherapy[18] on 3-week cycles until distant metastatic disease (0-1 week after post-chemotherapy evaluation)												Off Treatment[19, 23]
		C3D1	C3D2	C4D1	C4D2	C5D1	C5D2	C6D1	C6D2	C7D1	C7D2	C8D1	C8D2	
Visit Window[27]	-	+7		+7		+7		+7		+7		+7		+7
Cyclophosphamide		X		X		X		X		X		X		
GVAX			X		X		X		X		X		X	
Pembrolizumab		X		X		X		X		X		X		
Inclusion/Exclusion Criteria[24]	X													
Medications	X	X		X		X		X		X		X		X
Physical Exam	X	X		X		X		X		X		X		X
Vital Signs and pulse ox	X	X		X		X		X		X		X		X
Weight	X	X		X		X		X		X		X		X
Performance Status	X	X		X		X		X		X		X		X
Hematology profile[20]	X	X		X		X		X		X		X		X
Chemistry profile[20]	X	X		X		X		X		X		X		X
TSH[20,21]	X	X		X		X		X		X		X		X
Serum/Urine Pregnancy[26]	X	X		X		X		X		X		X		
CEA[20]	X	X		X		X		X		X		X		X
CA 19-9[20]	X	X		X		X		X		X		X		X
Adverse event evaluation	X	X		X		X		X		X		X		X
Vaccine Site Assessment				X		X		X		X		X		X
CT or MRI[22]	X							X						X
PBMC (up to 120cc)[25, 28]		X						X						X
Serum (up to 5cc) [25, 28]		X						X						X
Plasma (up to 20cc)[25, 28]		X						X						X
QoL Questionnaire		X						X						X

[18] Subjects will receive combination immunotherapy on a 21-day cycle. If subjects who have undergone surgical resection develop irAE precluding further pembrolizumab administration, they will still be eligible to continue with CY/GVAX monotherapy to complete the total of 8 cycles or until development of distant metastases. Unexpected Grade 3 or greater laboratory abnormalities should be repeated within 24-72 hours if clinically indicated and monitored as necessary to determine if event meets toxicity criteria.

[19] Approximately 30 days after their last dose of study drug or within 7 days prior to initiation of a new anti-cancer treatment, whichever comes first. Patients who discontinue from treatment should be contacted (by phone or email) every three months for up to 24 months or study closure to monitor overall survival. Information of other cancer therapies after discontinuation from the study treatment will be collected.

[20] Labs may be collected within a window of up to 3 days prior to dosing. Unexpected Grade 3 or greater laboratory abnormalities should be repeated within 24-72 hours if clinically indicated and monitored as necessary to determine if event meets toxicity criteria.

[21] T3 and FT4 to be checked reflexively if TSH is abnormal

[22] CT Chest, abdomen, pelvis with pancreas protocol with contrast or Non-contrast CT chest and MRI Abd, pelvis for those with contrast allergies

[23] Off study treatment visit for those patients not enrolling in the Extended Treatment Phase, otherwise patients will proceed to Extended Treatment Phase as per below

[24] Patients must have eligibility reconfirmed prior to initiation of Cycle 3 of immunotherapy. (Please see sections 3.3 and 3.4 for criteria).

[25] See section on correlative studies and lab manual for complete instructions

[26] For WOCBP. Pregnancy tests must be done within 7 days of the first treatment and then will be repeated with each subsequent therapy (collected within a window of up to 3 days prior to dosing).

[27] Longer delays to be approved by the PI and/or sponsor

[28] Research samples will be collected at the discretion of the PI based on availability of supplies and safety of patient and staff

In order to minimize the need for research-only in-person visits, telemedicine visits may be substituted for in-person clinical trial visits or portions of clinical trial visits where determined to be appropriate and where determined by the investigator not to increase the participants risks. Prior to initiating telemedicine for study visits the study team will explain to the participant, what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. Telemedicine acknowledgement will be obtained in accordance with the Guidance for Use of Telemedicine in Research. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions.

Procedure	Extended Treatment Phase: Pembrolizumab on 3-week cycle x 9 doses and Cy/GVAX on 24-week cycle x 4 doses[1]																Off Study[2]
	C1D1[10]	C2D1	C3D1	C4D1	C5D1	C6D1	C7D1	C8 D1 CY/GV AX Dose 1	CY/GV AX Dose 1 Day 2	C9D1	CY/GV AX Dose 2 Day 1	CY/GV AX Dose 2 Day 2	CY/GV AX Dose 3 Day 1	CY/GV AX Dose 3 Day 2	CY/GV AX Dose 4 Day 1	CY/GV AX Dose 4 Day 2	
Visit Window[11]	+7	+7	+7	+7	+7	+7	+7	+7		+7	+7		+7		+7		+7
Cyclophosphamide								X			X		X		X		
GVAX									X			X		X		X	
Pembrolizumab	X	X	X	X	X	X	X	X		X							
Physical Exam[13]	X	X	X	X	X	X	X	X		X	X		X		X		X
Vital Signs and pulse ox[3]	X	X	X	X	X	X	X	X		X	X		X		X		X
Weight	X	X	X	X	X	X	X	X		X	X		X		X		X
Performance Status	X	X	X	X	X	X	X	X		X	X		X		X		X
Hematology profile[4,5]	X	X	X	X	X	X	X	X		X	X		X		X		X
Chemistry profile[4, 6]	X	X	X	X	X	X	X	X		X	X		X		X		X
TSH[4, 7]	X	X	X	X	X	X	X	X		X	X		X		X		X
Serum/Urine Pregnancy[8]	X	X	X	X	X	X	X	X		X	X		X		X		
CEA[4]	X	X	X	X	X	X	X	X		X	X		X		X		X
CA 19-9[4]	X	X	X	X	X	X	X	X		X	X		X		X		X
Adverse event evaluation	X	X	X	X	X	X	X	X		X	X		X		X		X
Vaccine Site Assessment	X									X			X		X		X
CT or MRI[9, 14]	X			X			X				X		X		X		X
PBMC (up to 120cc)[12, 14]	X			X			X				X		X		X		X
Serum (up to 5cc)[12, 14]	X			X			X				X		X		X		X
Plasma (up to 20cc)[12, 14]	X			X			X				X		X		X		X
QOL Questionnaire	X							X			X		X		X		X

1. Pembrolizumab will be dosed on an every 21 day dosing, while cyclophosphamide/GVAX will be administered every 24 weeks. If subjects develop irAE precluding further pembrolizumab administration, they will still be eligible to continue with CY/GVAX monotherapy. Unexpected Grade 3 or greater laboratory abnormalities should be repeated within 24-72 hours if clinically indicated and monitored as necessary to determine if event meets toxicity criteria.
2. Approximately 30 days after their last dose of study drug or within 7 days prior to initiation of a new anti-cancer treatment, whichever comes first. Patients who discontinue from treatment should be contacted (by phone or email) every six months (+/- 1 month) for up to 24 months or study closure to monitor overall survival. Information of other cancer therapies after discontinuation from the study treatment will be collected. The off study scan do not need to be repeated if one has been performed within 6 weeks.
3. Temperature, respiration rate, blood pressure, pulse oximetry, and pulse should be taken at baseline, prior to pembrolizumab infusion, and at the end of the infusion.
4. Labs may be collected within a window of up to 3 days prior to dosing. Unexpected Grade 3 or greater laboratory abnormalities should be repeated within 24-72 hours if clinically indicated and monitored as necessary to determine if event meets toxicity criteria.
5. CBC with differential including absolute eosinophil count, absolute neutrophils, absolute lymphocytes, and platelets.
6. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
7. T3 and FT4 to be checked reflexively if TSH is abnormal.
8. For WOCBP. Pregnancy tests must be done within 7 days of the first treatment and then will be repeated with each subsequent therapy (collected within a window of up to 3 days prior to dosing).
9. CT Chest, abdomen, pelvis with pancreas protocol with contrast or Non contrast CT chest and MRI Abd, pelvis for those with contrast allergies. Imaging can be done one month before day 1 of each cycle.
10. Patients must have eligibility reconfirmed prior to initiation of Cycle 1 of extended treatment phase. (Please sections 3.3 and 3.4 for criteria).
11. Dosing visit window for extended treatment phase is -1/+7 days from prior dose of study drug. All labs must be collected within 3 days prior to dosing.
12. See section on correlative studies and lab manual for complete instructions
13. Patients should continue to have CT scan and evaluation with oncologist every 3 months of GVAX only therapy during Extended Treatment Phase (after Cycle 9 of Pembrolizumab)
14. Research samples will be collected at the discretion of the PI based on availability of supplies and safety of patient and staff

In order to minimize the need for research-only in-person visits, telemedicine visits may be substituted for in-person clinical trial visits or portions of clinical trial visits where determined to be appropriate and where determined by the investigator not to increase the participants risks. Prior to initiating telemedicine for study visits the study team will explain to the participant, what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. Telemedicine acknowledgement will be obtained in accordance with the Guidance for Use of Telemedicine in Research. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions.

10. MEASUREMENT OF EFFECT

10.1 Antitumor Effect – Solid Tumors

10.1.1 Definitions

Evaluable for toxicity. All subjects are evaluable for toxicity after receiving first dose of combined immunotherapy.

Evaluable for objective response. All patients who have received at least two doses of immunotherapy and have had their disease re-evaluated with imaging will be considered evaluable for response.

10.1.2 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. Subjects will be evaluated for anti-tumor effect by follow-up imaging (pancreas protocol CT, CT Chest/Abd/Pelvis, PET-CT imaging, and/or non-contrast CT chest and MRI Abd/pelvis) as outlined above. All subsequent scans (post-treatment) will be compared to the same pretreatment CT,PET/CT, or MRI that was used prior to initiating of study 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. 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.

10.1.3 Distant metastases free survival (DMFS)

DMFS is defined as the duration of time from start of treatment to identification of distant metastases on imaging or death, whichever occurs first. DMFS will be evaluated through 2 years from completion of trial. Individuals will be censored at the date of the last scan if no event occurs.

10.1.4 Overall Survival (OS)

OS is defined as the duration of time from start of study treatment to time of death. Individuals will be censored at the date of the last scan if no event occurs.

10.1.5 Local Progression-Free Survival (LPFS)

LPFS is defined as the duration of time from start of treatment to time of first documented local progression or death, whichever occurs first. Individuals will be censored at the date of the last scan if no event occurs.

10.2 Quality of Life

Quality of life will be assessed using the European Organization for Research and Treatment in Cancer quality of life core cancer questionnaire with the pancreatic cancer module (EORTC QLQ-C30/PAN26, **Appendix D**). The EORTC QLQ-C30 is a multidimensional, 30-item questionnaire, which assesses five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea/vomiting), a global health/QOL scale, as well as 6 single items.[39] The EORTC QLQ-PAN26 supplements the core questionnaire with 26 items specific for patients with pancreatic cancer.[40, 41] These instruments have been validated in patients receiving treatment for metastatic and resected pancreatic cancer and are sensitive to identify treatment related changes in quality of life.

11. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event guidelines and instructions for AE reporting can be found in **Section 6 (Adverse Events: List and Reporting Requirements)**.

11.1 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.

11.2 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.

Monthly teleconferences will be scheduled to include the Investigator and Merck representatives. During these meetings, the Investigator shall provide Merck with study progress updates. The Investigator will provide a summary of key points from the weekly meetings with a focus on safety of the protocol participants, enrollment status, and progress of data for objectives. In addition, Merck will provide safety and applicable program updates to the Sponsor.

11.3 Monitoring

This is a low risk study under the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center (SKCCC) Data Safety Monitoring Plan (DSMP, 2/21/19). Data monitoring of this protocol will occur on a regular basis with the frequency dependent on the rate of subject accrual and the progress of the study. The protocol will be monitored internally by the Principal Investigator. The protocol will be monitored externally by the SKCCC CRO in accordance with SKCCC guidelines. 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.

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 after each meeting. In turn, the study team will forward these summaries to the JHU and other participating site IRBs 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 IRB, JHU IBC, RAC, and the FDA immediately.

Dr. Jaffee will be holding the IND for this study. She will comply with all regulated reporting requirements to the FDA.

12. STATISTICAL CONSIDERATIONS

All statistical analyses will be performed using SAS® version 9 or higher or R version 3.0 or higher. All statements of statistical significance will be based upon a 2-tailed test with an overall 0.05 level of significance and all confidence intervals will be 95%.

Descriptive summaries for categorical variables will include counts and percentages. Descriptive summaries of continuous variables will include means, medians, standard deviations, and minimum and maximum values. Where applicable, comparisons between groups will be made using a Chi-square test or logistic regression for binary variables and analysis of variance (ANOVA) for continuous variables. Non-parametric alternatives such as Fisher's exact test or Kruskal-Wallis tests will be considered as need. Time to event outcomes will be analyzed using Kaplan-Meier estimates, log-rank tests, and Cox-proportional hazards models. Analysis for variables collected repeated over time (e.g. quality of life outcomes) will include paired t-tests and linear mixed effects models to account for the within-person correlation.

Additional post hoc statistical analyses not specified in the protocol, such as alternative modeling approaches may be completed.

12.1 Study Design/Endpoints

This is a single center, open-label, phase 2 study to evaluate the activity of combination pembrolizumab, CY, and GVAX in subjects with locally advanced pancreatic cancer in conjunction with chemotherapy, radiation therapy, and possible surgical therapy.

The primary endpoint is distant metastasis free survival (DMFS), which is defined above in **Section 10.1**.

Secondary endpoints include overall survival, immune-related local progression-free survival (LPFS), subsequent surgical resectability, pathologic response rates, and quality of life.

Exploratory endpoints include:

- IHC of immune parameters relevant to the PD-L1/PD-1 pathway
- Densities and distribution of T-cells in TME
- Transcriptional microarray analyses

- Peripheral antigen specific T-cell responses
- Intratumoral antigen specific T-cell responses

We will also evaluate safety and toxicity of combination pembrolizumab, CY, and GVAX. We will evaluate exploratory endpoints of pharmacogenomics and predictive biomarkers for responses.

12.2 Sample Size/Accrual Rate

Distant metastasis free survival (DMFS) is defined as the time from start of immunotherapy until distant recurrence or death, whichever occurs first. Individuals who do not experience an event will be censored at the date of the last scan. In the recent Phase II study, the median DMFS was 7.7 months (95% CI: 5.8-10.2) based upon 46 patients[7]. Assuming an enrollment period of 12 months and a minimum follow-up of 24 months (i.e. a total trial period of 3 years), a total of 54 evaluable participants in the new study will provide 80% power to detect an increase in median DMFS from the previously observed control rate of 7.7 months to 13.6 months (HR = 0.60) with a two-sided type I error rate of 0.05.

Participants in the current study will be considered evaluable if they have completed two doses of combination immunotherapy and have received a follow-up scan.

Each year, approximately 250 patients with newly diagnosed locally advanced pancreatic cancer are seen at JHH. Approximately, 50% of these patients will potentially be enrolled in clinical trials. We estimate that we could complete the accrual goal within one year. The expected number of events under the alternative hypothesis is 39.

12.3 Analysis of Primary Endpoints

The evaluable population includes all subjects who have completed at least two doses of combination immunotherapy and have received at least one follow-up scan.

Kaplan-Meier estimates of the survival function will be used to graphically display DMFS over time and to provide estimates of the median DMFS plus 1- and 2-year proportions. The new combination will be considered to have significantly increased DMFS if the lower bound of the 95% confidence interval of the median DMFS is above the observed control rate of 7.7 months. The effect of demographic, disease, and immunologic risk factors on DMFS will be evaluated using Kaplan-Meier estimates, log-rank tests, and Cox proportional hazards models.

Although not powered for direct comparison of the primary outcome, exploratory analyses comparing DMFS for the current trial and the recently completed phase II study used to determine the reference control will be performed. Log-rank tests and Cox proportional hazards models will be used to compare DMFS between studies.

We will include a preplanned subgroup analysis excluding those patients found to have metastatic disease intraoperatively that was not identified on pre-surgical imaging as they likely had existing metastatic disease and exact DMFS time period is indeterminate.

12.4 Analysis of Secondary and Exploratory Endpoints

As with the primary outcome, the evaluable populations includes all subjects who completed the initial round of chemotherapy treatment and received at least one follow-up scan. OS and LPFS (as defined in **Section 10.1**) will be analyzed using the techniques described for the primary outcome.

Subsequent surgical resectability will be determined by review of imaging and review of the subject's surgical candidacy (clinical status and tumor status) at our multi-disciplinary tumor board as per NCCN guidelines after completion of SBRT.[42] Pathologic response will be graded after surgical resection or biopsy with comparisons of pre-and post-immunotherapy core biopsies or surgical samples. For each outcome, the proportion will be calculated with an exact 95% confidence interval. Individuals who drop out of the study due to treatment toxicity or other causes prior to outcome assessment will be counted as not resectable and non-responders. Logistic regression will be used to assess the impact of risk factors on each outcome. Time to event analyses will be used to assess the timing of resection and response.

Quality of life will be assessed via EORTC QLQ-C30/Pan26 (v3.0) questionnaire. Our study population is pancreatic cancer subjects, and the analysis will be focused on Global Health Status/QoL scale, symptom scale (fatigue, pain), and functional scale (physical functioning, role functioning, emotional functioning) comparing data from initiation of treatment, with each immunotherapy, and after SBRT. For each module, summary statistics of the score will be reported as baseline and follow up time. Changes of quality of life score before and after treatment will be tested via paired t-test. In addition, mixed effect models will be fitted for assessing the pattern of quality of life over time. The frequency and proportion of patients who reach minimal clinically important difference (MCID) of 10-points change from baseline will be tabulated by time. Logistic mixed effects models will be used to track the proportion over time. The time to definitive deterioration in quality of life, defined as a decline of 10 points or more, will be analyzed using the Kaplan Meier method.

Genomic sequencing library construction, whole genome/exome sequencing, whole transcriptome sequencing, microbial sequencing, neoepitope prediction, mutation burden, and bioinformatic analysis will be performed either at an on-campus laboratory or at an off-campus sequencing service. All the samples will be de-identified before sending to any laboratory for sequencing. The FASTQ files, BAM files and VCF files will be generated and analyzed. Results from the sequencing studies will not be released to the patients. These studies are for research purposes only and are not using

a clinically validated platform.

Genomic sequencing data will be either destroyed or stored on a JHU managed, HIPAA-compliant, password protected hard drive or Johns Hopkins University School of Medicine PMAP.

12.5 Safety Analysis

The safety analysis will be performed in all treated subjects. A complete list of all AE data will be provided along with an assessment of grade and relationship to study drug. The incidence of AEs will be tabulated by subgroups of interest (e.g. grade 3 or higher, organ class, relationship to study drug). For analyses at the individual level, the highest grade and relationship to study drug will be assumed if multiple events have occurred. Toxicity will be tabulated by type and grade. Negative binomial regression and Cox proportional hazards models will be used to assess the rate and time to first toxicity, respectively.

12.5.1 Post-Operative Complications

The monitoring rule will focus on Grade IIIa post-operative complications or above, which is beyond what may be expected for chemotherapy or resection without immunotherapy, and that may be attributable to the immunotherapy drugs (any component of Cy/GVAX/Pembrolizumab). The proportion of subjects with post-operative complications (Grade IIIa or above) resulting from immunotherapy will be monitored using a Bayesian stopping guideline. A post-operative complications (Grade IIIa or above) level 40% would be considered the upper boundary for acceptable toxicity. We expect the actual post-operative complications (Grade IIIa or above) level to be approximately 26%. A Beta (2.5, 5.5) prior, representing a post-operative complications (Grade IIIa or above) rate of 31% (slightly above our expected rate), will be used to be conservative. After the first 6 patients have had surgery treatment, safety will be monitored continuously. If the posterior probability that the percentage of post-operative complications (Grade IIIa or above) exceeds 40% is greater than 0.5, then enrollment will be suspended until further review and consideration by the PI, IND Sponsor, and MEC. If the PI, IND sponsor and the surgical co-investigators determine that it is safe to do so (e.g. unrelated to study treatment, reversible/treatable complications), the trial may resume once updated treatment and monitoring plans have been developed and approved by the MEC, IRB and other oversite agencies. **Table 1** shows the number of post-operative complications (Grade IIIa or above) that would need to be observed in order to trigger the stopping guidelines throughout the course of the trial.

Table 1. The number of post-operative complications (Grade IIIa or above) needed to trigger stopping guidelines throughout the course of the study.

Number of Patients	Number of post-operative complications (Grade IIIa or above)needed to trigger re-evaluation
6-8	4
9-10	5
11-13	6
14-15	7
16-18	8
19-20	9
21-23	10
24-25	11
26-28	12
29-30	13
31-33	14
34-35	15
36-38	16
39-40	17
41-43	18
44-45	19
46-48	20
49-50	21
51-53	22
54	23

The probability of triggering the stopping guidelines was assessed for a range of possible true unacceptable surgical toxicity rates using simulations with 5000 replicates (**Table 2**). The probability of stopping to re-evaluate was 19.4% if the true proportion with an unacceptable immunotherapy toxicity was 26%, the expected value. In comparison, the probability of stopping early is 90% if the true proportion with an unacceptable immunotherapy toxicity was 45%, respectively.

Table 2. Probability of triggering a re-evaluation for a range of unacceptable post-operative complication rates (Grade IIIa or above).

True probability of unacceptable post-operative complications (Grade IIIa or above)	Number of post-operative complications (Grade IIIa or above)needed to trigger re-evaluation
5%	< 0.1%
10%	0.6%
15%	2.7%

20%	7.4%
26%	19.4%
30%	32.9%
35%	53.8%
40%	75.1%
45%	90.0%

12.6 Biomarker Analysis

Potential relationships between biomarker data and efficacy or safety endpoints will be investigated as part of an analysis plan aimed at identifying baseline biomarkers that may be used to prospectively identify subjects likely (or not likely) to respond to combination pembrolizumab, CY, and GVAX, and to identify subjects who may be predisposed to having adverse reactions to treatment. These exploratory predictive biomarker analyses will be completed with biomarkers measured in blood and in tumor samples and will focus on factors outlined in the exploratory objectives. Similar analyses will be completed with peripheral blood samples. We will also explore standard protein biomarkers such as CA19-9 and other exploratory circulating biomarkers. As with the primary outcome, the evaluable populations includes all subjects who completed the initial two cycles of immunotherapy and received at least one follow-up scan.

Comparison in pre- and post-treatment biomarker data will be compared using paired t-tests (or Wilcoxon signed rank tests if appropriate) and McNemar's tests for dichotomous or categorical variables. Associations between immune parameters will be explored graphically (e.g. scatterplots, boxplots) and numerically (e.g. correlations, Fisher's exact tests). Mixed effects models will be used to assess the patterns in biomarkers over time.

Efficacy measures will include OS and standard and immune criteria of response and PFS. Demographic and case-history factors will be examined to determine whether stratification or adjustments should be made within the subsequent statistical analyses, and if necessary, the appropriate stratification or adjustment will be made. Biomarkers will be summarized graphically as they relate to efficacy and safety endpoints, as applicable. Summary statistics will be tabulated. The relationships between binary measures (e.g. response) and time to event outcomes (e.g. OS) and candidate biomarkers will be investigated using logistic regression and Cox proportional hazards regression, respectively. Associations will be summarized in terms of point and interval estimates of hazard ratios, odds ratios, or other statistics, as appropriate for the analyses completed. Models to predict clinical activity based on combinations of biomarkers may also be investigated.

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APPENDIX A: 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 B: Adverse Event of Clinical Interest (ECI) Reporting Form

Adverse Event of Clinical Interest (ECI) Reporting Form

Please notify: IND Sponsor within 24 hours ([redacted]
Merck within 24 hours ([redacted])

Protocol Title:	Phase 2 Study of GM-CSF secreting allogeneic pancreatic cancer vaccine in combination with PD-1 Blockade Antibody (Pembrolizumab) for the Treatment of Patients with Locally Advanced Adenocarcinoma of the Pancreas		
Protocol Number (MK-3475-308):	**Signature of PI:**	**Principal Investigator:**	**Date:**

Report Type:

☐ **Initial** ☐ **Follow-up** ☐ **Final Follow-up** ☐ **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:**			**Action taken with the study drug:** ☐ **None** ☐ **Interrupted** ☐ **Discontinued** ☐ **Delayed**
	MK-3475	**CY**	**GVAX**	
	Date of Last Dose Prior to Event:			
	MK-3475	**CY**	**GVAX**	
	Number of Total Doses:			
	MK-3475	**CY**	**GVAX**	

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

Relationship to:	**MK-3475**	**CY**	**GVAX**	**Underlying Disease**
Unrelated	☐	☐	☐	☐
Probably Unrelated	☐	☐	☐	☐
Possible Related	☐	☐	☐	☐

Probably Related	☐	☐	☐	☐
Definitely Related	☐	☐	☐	☐

Section C: Brief Description of the Event: (please include relevant procedures and laboratory values)

Section D: Relevant Medical History

Section E: Concomitant Drug (Not related to ECI)

Name of the Drug	Start Date	Stop Date	Route	Dose	Frequency

Section F: Comments

Additional Documents: ☐ Please specify

APPENDIX C: SAE Reporting Form

Serious Adverse Event Reporting Form

Please notify: Dr. Jaffee within 24 hours ([redacted])
Merck within 24 hours ([redacted])

Protocol Title:	**Phase 2 Study of GM-CSF secreting allogeneic pancreatic cancer vaccine in combination with PD-1 Blockade Antibody (Pembrolizumab) for the Treatment of Patients with Locally Advanced Adenocarcinoma of the Pancreas**		
Protocol Number: (MK-3475-308)	**Signature of PI:**	**Principal Investigator:**	**Date:**
Report Type: ☐ **Initial** ☐ **Follow-up** ☐ **Final Follow-up** ☐ **Death** ☐ **Addendum to:**	**Serious Criteria (check all that apply):** ☐ Death ☐ Life-threatening ☐ Hospitalization or Elongation of Existing Hospitalization ☐ Persistent or Significant Disability ☐ Congenital Anomaly ☐ Other Important Medical Event ☐ Cancer ☐ Overdose	**Hospital Admission Date:** **Hospital Discharge Date:**	**Date Event Discovered:**

Section A: Subject Information

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

Section B: Event Information

Event diagnosis or symptoms:	**Date of First Dose:**			**Action taken with the study drug:**
	MK-3475	**CY**	**GVAX**	☐ **None** ☐ **Interrupted** ☐ **Discontinued** ☐ **Delayed**
	Date of Last Dose Prior to Event:			
	MK-3475	**CY**	**GVAX**	
	Number of Total Doses:			
	MK-3475	**CY**	**GVAX**	

Event Onset Date:	Event End Date:

Relationship to:	MK-3475	CY	GVAX	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 D: EORTC QLQ-C30/PAN26

ENGLISH

EORTC QLQ-C30 (version 3)

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

Please fill in your initials: _ _ _ _

Your birthdate (Day, Month, Year): _ _ _ _ _ _ _ _

Today's date (Day, Month, Year): 31 _ _ _ _ _ _ _ _

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

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

Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

EORTC QLQ - PAN26

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	**Not at all**	**A little**	**Quite a bit**	**Very much**
31. Have you had abdominal discomfort?	1	2	3	4
32. Did you have a bloated feeling in your abdomen?	1	2	3	4
33. Have you had back pain?	1	2	3	4
34. Did you have pain during the night?	1	2	3	4
35. Did you find it uncomfortable in certain positions (e.g. lying down)?	1	2	3	4
36. Were you restricted in the types of food you can eat as a result of your disease or treatment?	1	2	3	4
37. Were you restricted in the amounts of food you could eat as a result of your disease or treatment?	1	2	3	4
38. Did food and drink taste different from usual?	1	2	3	4
39. Have you had indigestion?	1	2	3	4
40. Were you bothered by gas (flatulence)?	1	2	3	4
41. Have you worried about your weight being too low?	1	2	3	4
42. Did you feel weak in your arms and legs?	1	2	3	4
43. Did you have a dry mouth?	1	2	3	4
44. Have you had itching?	1	2	3	4
45. To what extent was your skin yellow?	1	2	3	4
46. Did you have frequent bowel movements?	1	2	3	4
47. Did you feel the urge to move your bowels quickly?	1	2	3	4
48. Have you felt physically less attractive as a result of your disease and treatment?	1	2	3	4

Please go to the next page

During the past week:	**Not at all**	**A little**	**Quite a bit**	**Very much**
49. Have you been dissatisfied with your body?	1	2	3	4
50. To what extent have you been troubled with side-effects from your treatment?	1	2	3	4
51. Were you worried about your health in the future?	1	2	3	4
52. Were you limited in planning activities in advance (e.g. meeting friends)?	1	2	3	4
53. Have you received adequate support from your health care professionals?	1	2	3	4
54. Has the information given about your physical condition and treatment been adequate?	1	2	3	4
55. Have you felt less interest in sex?	1	2	3	4
56. Have you felt less sexual enjoyment?	1	2	3	4