**TITLE:** A Phase I/II trial of combination immunotherapy with nivolumab and a CCR2/CCR5 dual antagonist (BMS-813160) with or without GVAX following chemotherapy and radiotherapy for locally advanced pancreatic ductal adenocarcinomas (PDACs)

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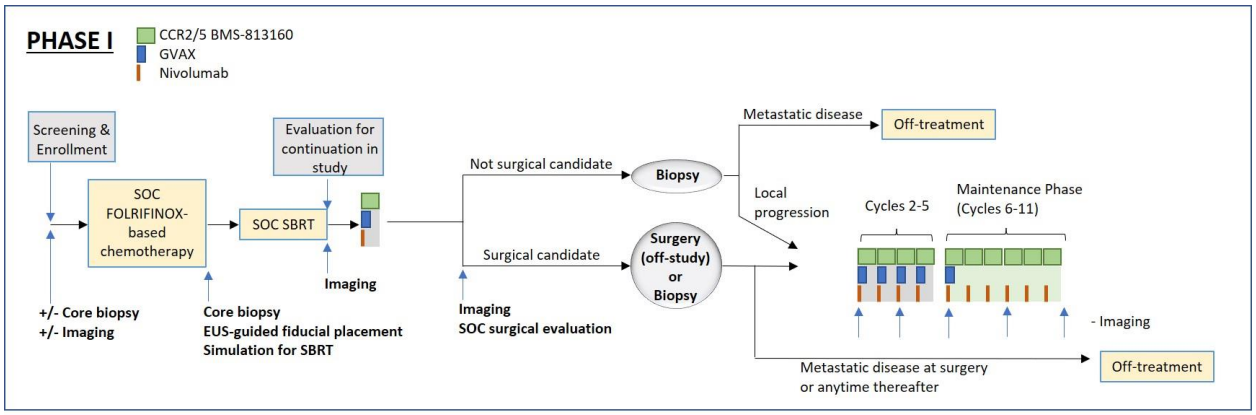
## SCHEMA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CCR2/5 BMS-813160
GVAX
Nivolumab
Screening & Enrollment
SOC FOLRIFINOX-based chemotherapy
SOC SBRT
Evaluation for continuation in study
Imaging
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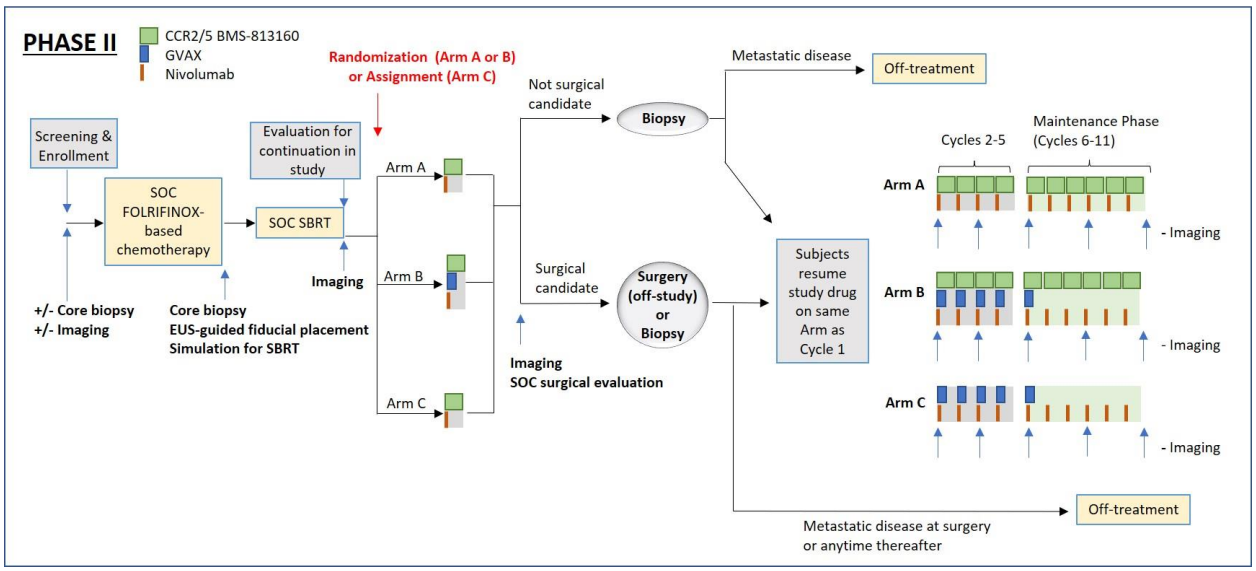
SOC surgical evaluation
Metastatic disease
Off-treatment
Local progression
Cycles 2-5
Maintenance Phase (Cycles 6-11)
- Imaging
Metastatic disease at surgery or anytime thereafter
Off-treatment


PHASE II
CCR2/5 BMS-813160
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Randomization (Arm A or B) or Assignment (Arm C)
Screening & Enrollment
SOC FOLRIFINOX-based chemotherapy
SOC SBRT
Evaluation for continuation in study
Imaging
+/- Core biopsy
+/- Imaging
Core biopsy
EUS-guided fiducial placement
Simulation for SBRT
Arm A
Arm B
Arm C
Not surgical candidate
Surgical candidate
Biopsy
Surgery (off-study) or Biopsy
Imaging
SOC surgical evaluation
Metastatic disease
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Subjects resume study drug on same Arm as Cycle 1
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- Imaging
Metastatic disease at surgery or anytime thereafter
Off-treatment

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# 1. OBJECTIVES

## 1.1 Primary Objectives

1.1.1 **Primary Objective in phase I portion of study:** To determine if the combination of nivolumab and a CCR2/CCR5 dual antagonist with GVAX is safe in patients with locally advanced pancreatic cancer (LAPC) who have received chemotherapy and radiotherapy.

1.1.2 **Primary Objective in phase II portion of study:** To determine if the combination of nivolumab and a CCR2/CCR5 dual antagonist with or without GVAX in patients with locally advanced pancreatic cancer (LAPC) who have received chemotherapy and radiotherapy enhances the infiltration of CD8+CD137+ cells in PDACs by comparing pre- and post-radiotherapy and immunotherapy treatment biopsies.

## 1.2 Secondary Objectives

1.2.1 **Secondary Objective in phase II portion of study:** To determine if the combination of nivolumab and a CCR2/CCR5 dual antagonist with or without GVAX is safe in patients with LAPC who have received chemotherapy and radiotherapy.

1.2.2 To determine the overall survival (OS) of patients with LAPC treated with chemotherapy and radiotherapy who subsequently receive nivolumab and a CCR2/CCR5 dual antagonist with or without GVAX compared to historical controls of patients treated with chemotherapy and radiation only and/or treated with GVAX plus anti-PD-1 antibodies.

1.2.3 To determine the metastasis free survival (MFS) of patients with LAPC treated with chemotherapy and radiotherapy who subsequently receive nivolumab and a CCR2/CCR5 dual antagonist with or without GVAX compared to historical controls of patients treated with chemotherapy and radiation only and/or treated with GVAX plus anti-PD-1 antibodies.

1.2.4 To determine the local progression free survival (LPFS) of patients with LAPC treated with chemotherapy and radiotherapy who subsequently receive nivolumab and a CCR2/CCR5 dual antagonist with or without GVAX compared to historical controls of patients treated with chemotherapy and radiation only and/or treated with GVAX plus anti-PD-1 antibodies.

1.2.5 To assess the surgical resectability rate of LAPC in subjects treated with chemotherapy and radiotherapy who subsequently receive nivolumab and a CCR2/CCR5 dual antagonist with or without GVAX compared to historical

controls of patients treated with chemotherapy and radiation only and/or treated with GVAX plus anti-PD-1 antibodies.

1.2.6 To assess the pathological response rate of subjects with LAPC in subjects treated with chemotherapy and radiotherapy who subsequently receive nivolumab and a CCR2/CCR5 dual antagonist with or without GVAX compared to historical controls of patients treated with chemotherapy and radiation only and/or treated with GVAX plus anti-PD-1 antibodies.

### 1.3 Exploratory Objectives

1.3.1 To evaluate the quality of life of subjects with LAPC in subjects treated with chemotherapy and radiotherapy who subsequently receive nivolumab and a CCR2/CCR5 dual antagonist with or without GVAX compared to historical controls of patients treated with chemotherapy and radiation only and/or treated with GVAX plus anti-PD-1 antibodies.

1.3.2 To evaluate the effects of the combination of nivolumab and a CCR2/CCR5 dual antagonist with or without GVAX and standard multimodality treatments upon the activation and expansion of T effector cells (Teffs) infiltrating into the tumor microenvironment (TME) compared to historical data of the TME in PDACs of patients treated with GVAX and nivolumab, and of patients treated with standard chemotherapy and SBRT.

1.3.3 To evaluate the tumor immune infiltrate [including tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSC), regulatory T-cells (Treg), CD4+OX40+, CD8+OX40+ cells] response after treatment with nivolumab and CCR2/CCR5 dual antagonist with or without GVAX and standard multimodality treatments compared to historical data of the TME in PDACs of patients treated with GVAX and nivolumab, and of patients treated with standard chemotherapy and SBRT.

1.3.4 To evaluate the immune parameters relevant to the activation of PD-L1/PD-1 associated immunosuppressive pathways, CCR2/CCR5/CXCR4 associated myeloid cell pathways and vaccine-induced immune regulatory signatures after treatment with nivolumab and CCR2/CCR5 dual antagonist with or without GVAX and standard multimodality treatments compared to historical data of the TME in PDACs of patients treated with GVAX and nivolumab, and of patients treated with standard chemotherapy and SBRT.

1.3.5 To evaluate mutated neoepitope specific T cell repertoire in pre- and post-treatment tumor specimens and in peripheral blood lymphocytes over time on treatment.

1.3.6. To monitor the peripheral and intratumoral antigen-specific T-cell responses after treatment with nivolumab and CCR2/CCR5 dual antagonist with or without GVAX and standard multimodality treatments.

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

1.3.8 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.

1.3.9 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.

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

## 1.4 Primary Endpoints

### 1.4.1 Primary Endpoint in phase I portion of study: Safety

- Study-related adverse events according to National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE; Version 5.0) that occur on or after Cycle 1, Day 1 immunotherapy.
- Incidence, nature and severity of all adverse events that occur on or after Cycle 1, Day 1.

### 1.4.2 Primary Endpoint in phase II portion of study: Immunologic

- Immune response, defined as >80% increase of infiltration of CD8+CD137+ T cell density after the first immunotherapy cycle (at the time of surgery or surgical evaluation if not a candidate) compared to baseline (prior to SBRT and after chemotherapy).
- Multiplex IHC staining of CD8+CD137+ cells in formalin-fixed, paraffin-embedded (FFPE) tissue slides of pre- and post-immunotherapy treatment PDAC biopsies. This will be analyzed by the Perkin-Elmer-Vectra multiplex immunofluorescent staining method.

## 1.5 Secondary Endpoints

### 1.5.1 Secondary Endpoint in phase II portion of study: Safety

- Study-related adverse events according to National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE; Version 5.0) that occur on or after Cycle 1, Day 1 immunotherapy.

- Incidence, nature and severity of all adverse events that occur on or after Cycle 1, Day 1.

### 1.5.1 Efficacy Endpoints

- OS from the time of Cycle 1, Day 1 of immunotherapy until death from any cause.
- MFS from the time of Cycle 1, Day 1 of immunotherapy until first documented distant metastases on imaging or death, whichever occurs first.
- LPFS from the time of Cycle 1, Day 1 of immunotherapy until first documented local progression on imaging or death, whichever occurs first.
- Surgical resectability determined by successful performance of resection (as defined by R0 and R1 resection).
- Pathologic response as determined by surgical margins and residual disease.

## 1.6 Exploratory/Correlative Endpoints

- Quality of life will be evaluated using the EORTC QLQ-C30/Pan26 questionnaire.
- Evaluate changes in CD4+OX40+ and CD8+OX40+ cell density in pre- and post-treatment specimens via Halo-analysis.
- Evaluate changes in the expression of CCR2, CCR5, CXCR4 and PD-L1/PD-1 pathways in pre- and post-treatment specimens by nanostring analysis.
- Evaluate changes in M1 vs. M2 TAM, Teff:Treg, and MDSC by multiplex IHC.
- Evaluate mutated neoepitope specific T cell repertoire by TCR clonality and/or the MANAFEST assay in pre- and post-treatment tumor specimens and in peripheral blood lymphocytes over time on treatment.
- Cytokine/chemokine assays to assess changes in intratumoral inflammatory markers
- 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

## 1.7 Study Design

This is a single-center, open label, phase I/II clinical trial to evaluate the immune effects, safety and clinical activity of the combination of nivolumab and CCR2/CCR5 dual antagonist with or without GVAX in patients who have received standard chemotherapy and stereotactic body radiation therapy (SBRT) for LAPC.

Patients who have a new diagnosis of untreated LAPC will be eligible for enrollment. We will consent patients at the time of diagnosis of LAPC based upon criteria from NCCN Guidelines as determined by review of imaging and pathology at our institution. If the patient has not had a diagnostic core biopsy adequate for review by our institution, an on-study core diagnostic biopsy will be performed. If the patient's available imaging is not adequate for review by our institution, repeat imaging will be performed. The patient will also undergo blood draws at the time of screening and enrollment. After completing all screening procedures and meeting eligibility criteria, the patients will then receive FOLFIRINOX-based induction chemotherapy and SBRT. Chemotherapy and radiotherapy are considered standard therapy. Chemotherapy may be administered at any facility, but SBRT treatment will be performed at Johns Hopkins. Of note, patients should meet all eligibility criteria and have all screening procedures completed prior to initiating chemotherapy, however they may be enrolled up to one month after beginning SOC chemotherapy to allow for time to collect records from outside institutions if necessary. Only toxicities considered related to study procedures or treatment will be collected during this period. The patients should receive at least eight and no more than sixteen 14-day cycles of FOLFIRINOX-based chemotherapy. After completion of chemotherapy, the patients will undergo EUS-guided fiducial placement along with a post-chemotherapy core biopsy of the pancreas tumor, blood draws to evaluate for circulating tumor cells and other inflammatory markers and an SBRT simulation. We will not confirm presence of tumor in the post-chemotherapy core biopsy since some patients may not have persisting tumor; the biopsy is to evaluate the tumor microenvironment. SBRT will be initiated (6.6 Gy x 5 days) approximately two to four weeks after completion of chemotherapy.

After completion of SBRT, the patients will then be re-evaluated for eligibility for continuation in the study and must have LAPC based on NCCN Guidelines as determined by review of CT, PET, or MRI imaging at our institution. Patients who have developed metastatic disease are no longer eligible to continue in the study. If the patients remain eligible for continuation in the study after rescreening, they will be assigned or randomized to a study arm (depending on when they were enrolled).

Due to availability of BMS-813160, study enrollment was closed as of December 19, 2022. Patients randomized prior to this will continue receiving study treatment as planned until drug supply expires on July 31, 2023, then will continue to receive any remaining study cycles without BMS-813160. Any patients who were enrolled but not randomized prior to December 19, 2022 (i.e. those receiving chemotherapy) will be assigned to a new arm (Arm C).

In phase I, the combination immunotherapy consists of nivolumab, CCR2/CCR5 dual-antagonist (BMS-813160) and GVAX. In phase II, the first 10 patients will be randomized 1:1 between Arm A and Arm B. Remaining patients will be assigned to Arm C.

Arm A subjects receive nivolumab and BMS-813160, Arm B subjects receive nivolumab, BMS-813160, and GVAX, and Arm C patients will receive nivolumab and BMS-813160 for Cycle 1 (prior to surgery) and then nivolumab and GVAX for Cycles 2 and beyond.

After randomization or assignment to a study arm, subject will receive Cycle 1 of the combination immunotherapy. Cycle 1 lasts 28 days and will start within two weeks of completion of SBRT.

Surgery will be scheduled to occur between five to seven weeks after completion of SBRT. If surgery is scheduled more than 28 days from the start of Cycle 1, anti-CCR2/5 therapy will be continued up to the day before surgery (but a second dose of nivolumab and GVAX will not be administered because this is not considered a new cycle). Standard surgical procedure will be determined by the operating surgeon. Surgery is considered standard of care and must be performed at Johns Hopkins. Only toxicities considered related to study procedures or treatment will be collected from the time of surgery until the start of Cycle 2. Post-treatment biospecimens will be obtained intraoperatively for resectable patients. If the patient is found to have an unresectable tumor during surgery, research core biopsies will be obtained intraoperatively. For patients who are not surgical candidates, they will undergo an EUS-guided tumor biopsy.

Both resected (estimated 30-40%) and unresected patients will receive combination immunotherapy every 28 days for a total of 4 more cycles or until the development of metastatic disease. For those who undergo a surgery or NanoKnife procedure, immunotherapy will be initiated within 6 to 12 weeks of the procedure. For those who are not surgical candidates, the immunotherapy will not be held. Patients with local progression will be allowed to continue the study treatment. Participants who develop metastatic disease after the initiation of immunotherapy will go off trial, but they will be offered biopsy of the metastatic lesions if they can be safely biopsied (as determined by our interventional radiology team). Patients will be expected to be on trial for approximately 7 to 9 months if they undergo surgery, and approximately 6 months if they do not undergo surgery.

Following the 4 cycles of immunotherapy post-surgical evaluation, if the patient remains free of metastatic disease, the patient will have the option of receiving maintenance immunotherapy. During the maintenance portion of the study, Phase I or Phase II Arm B patients will receive BMS-813160 given bi-daily for 24 weeks, nivolumab every 4 weeks for a total of six 28-day cycles, and GVAX given once on Cycle 1 Day 2. Phase II Arm A patients will receive BMS-813160 bi-daily for 24 weeks, and nivolumab every 4 weeks for a total of six 28-day cycles. Phase II Arm C patients will receive nivolumab every 4 weeks for a total of six 28-day cycles, and GVAX once on Cycle 1 Day 2.

The primary endpoint of Phase I is safety, and the primary endpoint of Phase II is the degree of CD8+CD137+ T-cells infiltration in pre- and post-immunotherapy tumor specimens. Individuals will be censored at the date of last scan if no event has occurred. Secondary endpoints are OS, MFS, LPFS, surgical resectability, and pathologic response and as defined above. Exploratory endpoints include quality of life and immunologic, genetic/molecular and biomarker analysis, some of which will be correlated with clinical outcomes.

The Phase I portion is a 3+3 dose-escalation design to determine the maximum tolerated dose (MTD) or recommended phase 2 dose of BMS-813160 for use in the combination. It will evaluate two dose levels and enroll 3 to 12 patients depending on the number of dose limiting toxicities (DLT). All patients in Phase I portion will receive nivolumab, CCR2/CCR5 dual-antagonist (BMS-813160) and GVAX. DLT evaluation interval is the first cycle of treatment, beginning on the first day of treatment.

The MTD will be determined using the following escalation rules:

- A cohort of three patients will be entered at each dose level.
- If none of the subjects has a DLT during their first cycle, then the dose will be escalated and subjects will be enrolled at the next dose level.
- If 1 of 3 subjects at a given dose level has a DLT during the first cycle, then 3 additional subjects will be enrolled at the same dose level. Dose escalation will only occur if no additional DLTs are observed in the 3 additional subjects after they have been followed for one cycle of treatment.
- If 2 or more subjects at a dose level have a DLT during the first cycle, dose escalation will cease, and this dose level will have exceeded the MTD. New subjects will be enrolled at next lower dose level until that cohort has 6 subjects.
- A total of 6 patients must be enrolled at a dose level in order to declare MTD.
- The MTD will be defined as the dose of BMS-813160 in the combination in which $< 2$ of 6 patients experiences a DLT with the next higher dose having at least 2 of 3 or 2 of up to 6 patients experiencing a DLT.
- If $\leq 1$ in 6 patients experience DLT at dose level 2, dose escalation will stop and this dose level will be the recommended dose for Phase II.

The Phase II portion is a randomized two-arm study to evaluate immune response, efficacy and safety of the combination of nivolumab and CCR2/CCR5 dual-antagonist (BMS-813160) with and without GVAX. We will be monitoring the toxicities for each arm in the Phase II portion, and if we observe >33% unacceptable toxicities in the first 6 patients or any time afterwards in any arm, we will halt the enrollment pending safety evaluations.

DLTs will be assessed in the first cycle of Phase I, starting Cycle 1 Day 1 through prior to initiation of Cycle 2. Unacceptable toxicities will be used to monitor safety from Cycle 2 Day 1 of Phase I through to end of study treatment and from Cycle 1 Day 1 of Phase II through to end of treatment. During periods of standard of care treatment (FOLFIRINOX-based chemotherapy, SBRT, Surgery) only AEs considered related to study treatment will be collected. If patients develop adverse events (AEs) to any of the three immunotherapies

(BMS-813160, nivolumab or GVAX) leading to its/their discontinuation, they will be taken off the trial.

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) to evaluate for local progression and metastatic disease while they are on study.

## 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. 79% of even those who receive treatment will eventually succumb to recurrent disease.[2] In addition, the vast majority 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 in LAPC improve local control and increase the likelihood of a margin-negative resection (ECOG 4201).[3] Induction chemotherapy followed by chemoradiation results 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, delays full-dose chemotherapy, is given with low 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 in 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 and 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] _ENREF_7 GM-CSF is an important cytokine in inducing the growth and differentiation of dendritic cells, which act as antigen-presenting cells for tumor antigens. Autologous GM-CSF secreting vaccines have shown immune activation in 10-40% of treated patients 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] Patients 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 delayed type hypersensitivity (DTH) responses observed in 1 of 3 patients receiving $1 \times 10^8$ and in 2 of 5 patients receiving $5 \times 10^8$ 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 and 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.[15-18] Murine breast cancer models treated with CY prior to vaccination showed an immune enhancing effect with suppression of Treg and increase in effector T-cells.[19] In a phase II trial for treatment of 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 occurring in only one of 30 patients.[20] Median survival was 2.3 months versus 4.7 months in

patients receiving GVAX without and with CY, respectively. Pathologic evaluation revealed that there was a trend toward prolonged progression-free survival in patients who had persistent mesothelin-specific T-cell responses with immunotherapy.

In an ongoing neoadjuvant and adjuvant trial of CY/GVAX in patients with resectable pancreatic cancer (NCT01088789), 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 and organized lymph node-like structures, with suppression of the Treg pathway, that were not observed in tumor tissue resected from unvaccinated patients.[21]

The activated T-cells infiltrating the tumor secrete interferon-γ, which in turn upregulates the PD-1/PD-L1 pathway.[21,22] These data support an emerging concept that vaccines are required to induce a T-cell response that is capable of infiltrating the TME. However, vaccination is just the first step toward establishing an effective antitumor immune response, converting the PDAC TME into an environment similar to what is observed in melanomas, exhibiting infiltrating but immunosuppressed T-cells prior to immunotherapy treatment. Thus, we hypothesize that treatment with GVAX primes the PDAC TME for anti-PD-1/PD-L1-targeted therapy. Supporting this hypothesis, we have demonstrated in a preclinical model of PDAC that combining anti-PD-1 and anti-PD-L1 antibodies with CY/GVAX enhances the infiltration of effector T-cells into PDAC tumors as well as the cure rate in PDA tumor-bearing mice.[22]

### 2.4 anti-PD1/PDL1 blockade [Nivolumab (Opdivo, BMS-936558)]

The importance of an intact immune surveillance system for controlling neoplastic transformation has been known for decades.[23] There is accumulating evidence correlating tumor-infiltrating lymphocytes (TILs) in cancer tissue to 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 melanoma and renal cell carcinoma (RCC). TILs can be expanded *ex vivo* and re-infused, inducing durable objective tumor responses in cancers such as melanoma.[24, 25]

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1 (CD279), a Type I transmembrane protein of the CD28 family of T-cell receptors and expressed on the cell surface of activated T-cells and B-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.[26-29] 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 detectable 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.[26] Although healthy organs express little (if any) PD-L1, a variety of cancers have been shown to express abundant levels of this T-cell inhibitor. High expression of PD-L1 on tumor cells (and PD-L2 to a lesser extent) has been found to correlate with poor prognosis and survival in various cancer types, including RCC,[30] pancreatic carcinoma,[31] hepatocellular carcinoma[32] and ovarian carcinoma.[33] Furthermore, PD-1 has been suggested to regulate tumor-specific T-cell expansion in patients with malignant melanoma.[34] 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.

Nivolumab 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. Nivolumab enhances T-cell proliferation, and in a mixed lymphocyte reaction, it produces a producible concentration-dependent increase of interferon-gamma (IFN-γ) release in vitro. Nivolumab also demonstrated CMV antigen-specific recall responses in an assay using human peripheral blood mononuclear cells from a CMV-exposed donor, with augmented IFN-γ secretion from CMV-specific memory T-cells in a dose-dependent manner up to 10 μg/mL. The anti-tumor effects of anti-PD-1 has been observed in several murine models of both PD-L1 and PD-L2. In addition, in tumor models that are resistant to anti-PD-1 therapy, such as pancreatic cancer, the combination with vaccines or other immunomodulatory antibodies improves therapeutic efficacy as described above.[22]

The overall safety experience of nivolumab, as either monotherapy or in combination with other therapies, is based on approximately 12,300 participants. Most adverse events (AEs) were low-grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. There was no pattern in the incidence, severity, or causality of AEs with respect to nivolumab dose. Nivolumab is FDA-approved for treating unresectable or metastatic melanoma, metastatic non-small cell lung cancer, advanced renal cell carcinoma, classical Hodgkin lymphoma, recurrent or metastatic squamous cell carcinoma of the head and neck, locally advanced or metastatic urothelial carcinoma, MSI-h or dMMR metastatic colorectal cancer and hepatocellular carcinoma.

Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. Nivolumab has no antibody-dependent-cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) activity, and also has no cross-reactivity to other members of the CD28 family of T-cell receptors. Nivolumab is not expected to promote non-specific activation of lymphocytes. Nivolumab is not expected to have any effect on cytochrome P450 or other drug metabolizing enzymes, and is expected to undergo in vivo degradation into small peptides and amino acids via biochemical pathways independent of drug metabolism enzymes.

The FDA-approved Q4W dose of Nivolumab is 480 mg IV given every 4 weeks will be used in this study.

## 2.5 CCR2/CCR5 dual antagonism (BMS-813160)

Our multiplex immunohistochemistry analysis of surgical PDAC specimens from patients who received neoadjuvant GVAX showed that low myeloid infiltration into the tumor was associated with better overall survival compared to those with high myeloid infiltration.[35] RNA microarray analysis of the lymphoid aggregates after microdissection demonstrated that CCL2 expression in the lymphoid aggregates is significantly associated with poorer survival following treatment with GVAX.[21]

CCR2 and its cognate ligand CCL2 have been implicated in tumor infiltration by immunosuppressive cells, notably M2 (pro-tumor) tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs). CCR2 is more specifically expressed in PDACs, and not in normal pancreatic tissues (*The Human Pathology Atlas*). Human pancreatic cancer produces CCL2, and immunosuppressive CCR2+ macrophages infiltrate these tumors. Patients with tumors that exhibit high CCL2 expression/low CD8 T-cell infiltrate have significantly decreased survival.[36] In mice, CCR2 blockade depletes inflammatory monocytes and macrophages from the primary tumor and pre-metastatic liver resulting in enhanced antitumor immunity, decreased tumor growth and reduced metastasis. Our collaborator on the CCR2 preclinical project (Dr. Yangxin Fu, UT Southwestern) found that CCR2 blockade synergized with radiation for anti-tumor activity by targeting CCR2+ M-MDSC.

Antagonism of CCL2's receptor, CCR2, has been tested in multiple clinical trials, and likely exerts its effects through targeting CCR2+ myeloid cells. For instance, BMS-813160, a dual antagonist of CCR2/CCR5, was investigated in a phase II clinical trial by Bristol-Myers Squibb for the treatment of diabetic nephropathy. A phase I/II study of BMS-813160 in combination with chemotherapy or nivolumab in patients with advanced solid tumors has demonstrated no dose-limiting toxicities in Part 1 of the study, and a dose of 300 mg BID has been chosen for BMS-813160 for Part 2 of the study based on safety, PK and PD seen in Part 1. Therefore, CCL2 expression in vaccine-induced lymphoid aggregates is potentially targetable through inhibiting its receptor, particularly with BMS-813160.

CCR5 is another chemokine receptor that plays a role in the infiltration of Treg and TAM into tumors,[37] and is another potential target for inhibition. CCR5 and CXCR4 form a heterodimer that regulates T-cell function,[38] [redacted] Furthermore, the combination of anti-CXCR4, anti-PD1 and GVAX was associated with statistically significant improved survival compared to the GVAX/anti-PD-1 treatment group in the same pre-clinical model. Doug Fearon's group also showed that administering AMD3100, a small molecular inhibitor of CXCR4, induced rapid T-cell accumulation in PDACs and acted synergistically with anti-PD-L1 antibody to diminish tumors in the PDAC bearing mice.[39] However, CXCR4 expression is heterogeneous in PDACs, and CXCR4 is expressed by multiple cell types including tumor

epithelial cells, lymphocytes and myeloid cells. Therefore, directly targeting CXCR4 in PDACs may not be an optimal option, and inhibition of CXCR4 by way of CCR2 antagonism may be a better-targeted option.

Our pre-clinical findings and currently known therapeutic effects of dual CCR2/CCR5 inhibition suggest that dual antagonism is a powerful treatment option.

BMS-813160 was previously evaluated in four clinical trials and found to be relatively safe and well-tolerated across a wide dose range, in both 108 healthy participant and in 59 participants with diabetic kidney disease (DKD) who received at least one dose of BMS-813160.[40] BMS-813160 at doses ≥ 300 mg BID results in sustained inhibition of CCR2 and CCR5 on day 14, and also was safe and well-tolerated in both healthy participants and patients with DKD. The combination of nivolumab, GVAX and BMS-813160 may cause more immune-mediated adverse events than when each therapy is given alone. For this reason, in this study, we will use two dose levels: 150 mg PO BID for dose level 1 and 300 mg PO BID for dose level 2.

## 2.6 Preclinical and Clinical Trial Data

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

## 2.7 Rationale

There is no standard of care established for locally advanced, unresectable pancreatic cancer (LAPC), and its prognosis remains grim. A combination of chemotherapy and radiation appeared to be particularly effective in LAPC by improving local control and increasing the likelihood of a margin-negative resection.[3] Induction chemotherapy followed by chemoradiation result in better outcomes when compared to other treatment sequences.[4] 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.[6,7]

The addition of immunotherapy to chemoradiation is also a promising avenue. As described above (in **Section 2.5**), CCR2 inhibition was found to enhance radiosensitivity in mouse tumor models. In addition, targeting tumor-associated macrophages with CCR2 inhibition in combination with FOLFIRINOX in patients with borderline resectable and locally advanced pancreatic cancer was tested in a single-center, open-label, dose-finding, non-randomized, phase 1b trial.[41] The results are deemed promising, with 16 (49%) of 33 patients receiving FOLFIRINOX plus CCR2 inhibitor (PF-04136309) who had undergone repeat imaging achieved an objective tumor response, with local tumor control achieved in 32 (97%) patients. In contrast, none of the five patients in the FOLFIRINOX alone group achieved an objective response on repeat imaging, although four (80%) of those patients achieved stable disease.

GVAX administration has been shown to activate the tumor microenvironment (TME) in preclinical models by diminishing Tregs and increasing interferon-γ secreting Teffs, but it also upregulates the PD-1/PD-L1 pathway.[21,22] In our completed first neoadjuvant immunotherapy window-of-opportunity study of pancreatic cancer with GVAX, we demonstrated that resected PDACs contained vaccine-induced tertiary lymphoid aggregates with the induction of PD-L1/PD-1 expression.[21] In a preclinical model of PDAC, 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 increased cure rate in PDAC tumor-bearing mice.[22] Accordingly, a second neoadjuvant clinical study testing the combination of nivolumab and GVAX is ongoing. Additionally, CCL2 expression in the lymphoid aggregates and high myeloid infiltration into the PDAC were associated with poorer survival following GVAX treatment. Targeting myeloid cells in the preclinical models showed an increase in CD8+ T-cells expressing activation markers such as 4-1BB/CD137 and OX40. The CCR2/CCR5 dual antagonist is believed to target pro-tumor myeloid cells and is currently being tested in a phase Ib/II clinical trial in combination with nivolumab or chemotherapy. In the meantime, in unresectable metastatic PDACs, the combination of nivolumab and vaccine therapies demonstrated objective responses, however, with delayed onset and short duration (Le et al. Personal communication).

Therefore, we now propose the third preoperative immunotherapy study to test the combination of GVAX, anti-PD-1 antibody (nivolumab) and CCR2/CCR5 dual antagonist (BMS-813160) for locally advanced pancreatic cancer, where one cycle of combination immunotherapy is given following induction chemotherapy and SBRT, but before surgical re-evaluation for possible resection. Following the surgical resection or if the patient remains ineligible for the surgical resection, the patients will continue to receive the combination immunotherapy up to 4 more cycles until development of metastasis. Cyclophosphamide will not be administered in this study because we anticipate that CCR2/5 inhibition will lead to decreased Treg, which was the observed effect of cyclophosphamide in our previous studies.

# 3. PATIENT SELECTION

## 3.1 Eligibility Criteria for Initial Enrollment into Study

3.1.1 Patients with histologically- or cytologically-proven, surgically unresectable, locally advanced pancreatic adenocarcinoma (at diagnosis) by NCCN guidelines, as determined by review of imaging and pathology at our institution.

3.1.2 If the patient does not have a diagnostic biopsy that is adequate for review at our institution, the patient must agree to a research core biopsy to be performed at Johns Hopkins.

3.1.3 If the patient's available imaging is not adequate for review by our institution, the patient must agree to a repeat imaging to be performed at Johns Hopkins.

3.1.4 Age $\geq$18 years.

3.1.5 ECOG performance status 0-1 (**Appendix A**).

3.1.6 Life expectancy greater than 3 months.

3.1.7 Able to swallow pills or capsules and tolerate oral medication.

3.1.8 Patients must be eligible to receive FOLFIRINOX-based chemotherapy per treating (can be non-study) medical oncologist.

3.1.9 Patients must be willing to be treated with stereotactic body radiation therapy (SBRT) and undergo surgery (if deemed a surgical candidate) only at Johns Hopkins Hospital.

3.1.10 Patients must be willing to undergo a core biopsy of the pancreatic cancer during EUS-guided fiduciary placement at Johns Hopkins Hospital.

3.1.11 Patients must be willing to undergo a biopsy of the pancreatic cancer at Johns Hopkins Hospital if the patient is not deemed a surgical candidate during the pre-surgical evaluation.

3.1.12 Patients must inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.

3.1.13 Female patient of childbearing potential (WOCBP) (defined below) must have a negative urine or serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]). If the urine test is

positive or cannot be confirmed as negative, a negative serum pregnancy test will be required for the patient to be eligible. If a patient has a positive serum pregnancy test, then an ultrasound must be done to rule out pregnancy to enroll on trial.

- A woman is considered of childbearing potential (WOCBP) following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
- Women in the following categories are not considered WOCBP:
  - Pre-menarchal
  - Pre-menopausal female with one of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy or tubal ligation
    - Documented bilateral oophorectomy
  - Postmenopausal female - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.

3.1.14 WOCBP must use one of the highly effective methods of contraception (which have a failure rate of < 1% when used consistently and correctly) listed here during study duration and through 5 months after the end of study treatment. Approved contraceptive methods include combined (estrogen- and progestogen-containing) hormonal contraception (oral, intravaginal, transdermal), progestogen-only hormonal contraception (oral, injectable), implantable progestogen-only hormonal contraception, other hormonal methods of contraception (vaginal ring, injectables, implants and intrauterine hormone-releasing system), intrauterine device and bilateral tubal occlusion.

A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant. It is not necessary to use any other method of contraception when complete abstinence is elected. WOCBP participants who choose complete abstinence must continue to have pregnancy tests. Acceptable

alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence.

The following are unacceptable methods of contraception:

- Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously
- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal Sponge with spermicide
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action
- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus).
- Spermicide only
- Lactation amenorrhea method (LAM)

3.1.15 Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until 7 months after the end of study treatment.
- Female partners of males participating in the study to consider use of effective methods of contraception until 7 months after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 7 months after the end of study treatment.
- Refrain from donating sperm for the duration of the study treatment and until 7 months after the end of study treatment.
- Confirmed azoospermic males are exempt from contraceptive requirements.

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

## 3.2 Exclusion Criteria for Initial Enrollment into Study

### Prior Therapy

3.2.1 Patients cannot have had any prior therapy for the locally advanced pancreatic adenocarcinoma prior to signing informed consent form

*Patients will be allowed to enroll on trial up to one month after initiating the SOC FFX described in this study as long as all other eligibility criteria have been met

3.2.2 Patients with a history of past treatment with immunotherapy agents prior to initial enrollment into this study (including, but not limited to: IL-2, interferon, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-OX-40, anti-CD40, anti-CTLA-4 or anti-CCR2/5 antibodies).

3.2.3 Patients with prior organ or tissue allograft, including corneal allograft, or allogeneic bone marrow transplantation. Exceptions can be approved by the IND Sponsor if loss of the graft is not a clinical concern.

3.2.4 Is currently participating or has participated in a study of an investigational agent or using an investigational device for the treatment of cancer. The Principal Investigator must approve the patient's participation in other clinical trials.

**Medical History and Concurrent Diseases**

3.2.5 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.

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

3.2.7 Requires the use of home oxygen.

3.2.8 Uncontrolled or significant cardiovascular disease including, but not limited to, any of the following:

- Myocardial infarction or stroke/transient ischemic attack within the past 6 months
- Uncontrolled angina within the past 3 months
- Any history of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes)
- History of other clinically significant heart disease (eg, cardiomyopathy, congestive heart failure with New York Heart Association functional classification III-IV, pericarditis, significant pericardial effusion, or

myocarditis)
- Cardiovascular disease-related requirement for daily supplemental oxygen therapy

3.2.9 Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome.

3.2.10 History of any chronic hepatitis as evidenced by the following:
- Positive test for hepatitis B surface antigen
- Positive test for qualitative hepatitis C viral load [by polymerase chain reaction (PCR)]

  Note: Participants with positive hepatitis C antibody and negative quantitative hepatitis C by PCR are eligible. History of resolved hepatitis A virus infection is not an exclusion criterion.

3.2.11 Any concurrent malignancy other than non-melanoma skin cancer, non-invasive bladder cancer, early stage prostate cancer, or carcinoma in situ of the cervix. Patients with a previous non-pancreatic, non-periampullary malignancy without evidence of disease for > 2 years will be allowed to enter the trial.

3.2.12 Other uncontrolled intercurrent illness including, but not limited to, chronic ongoing infection or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.13 Current or recent (within 3 months of study treatment administration) gastrointestinal disease that could impact the absorption of study treatment.

3.2.14 Any gastrointestinal surgery that is likely impact upon the absorption of study treatment.

3.2.15 Inability to be venipunctured and/or tolerate venous access.

**Physical and Laboratory Test Findings**

3.2.16 Ascites needing paracentesis or medical management.

**Allergies and Adverse Drug Reaction**

3.2.17 History of severe hypersensitivity reaction to any monoclonal antibody.

3.2.18 History of allergy to study treatments or any of its components of the study arm that participant is enrolling.

3.2.19 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.

**Other Exclusion Criteria**

3.2.20 Women who are pregnant or breastfeeding.

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

## 3.3 Eligibility Criteria for Continuation in Study and Initiation of Immunotherapy

Patients must have eligibility checked prior to initiation of combination immunotherapy, and must meet the following criteria for continued participation in the study.

3.3.1 Patients must have received 8-16 14-day cycles of FOLFIRINOX-based chemotherapy (i.e. FOLFIRINOX, 5-FU/leucovorin, FOLFIRI). Patients may have received Gemcitabine/Abraxane due to intolerance of FOLFIRINOX, but cannot have switched chemotherapy regimens due to progression or lack of response.

3.3.2 Patients must have completed SBRT (recommend 6.6 Gy x 5 days) at Johns Hopkins Hospital.

3.3.3 All toxicities attributed to prior anti-cancer therapy other than alopecia, fatigue, and hematologic lab abnormalities must have resolved to Grade 1 (NCI CTCAE v5.0) or baseline before administration of study treatment.

Participants with toxicities attributed to prior anti-cancer therapy that are not expected to resolve and result in long lasting sequelae, such as neuropathy or alopecia after platinum-based therapy, are permitted to enroll.

3.3.4 ECOG performance status 0-1 (**Appendix A**).

3.3.5 Able to swallow pills or capsules and tolerate oral medication.

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

| | |
|---|---|
| White blood cell count | $\geq$ 2,000 cells/mm$^3$ |
| Absolute lymphocyte count | $\geq$ 500 cells/mm$^3$ |
| Absolute neutrophil count | $\geq$ 1,000 cells/mm$^3$ |
| Hemoglobin | $\geq$ 9 g/dL* |
| Platelets | $\geq$ 80,000 cells/mm$^3$* |
| AST and ALT | $\leq$ 3 x ULN |
| Total bilirubin | $\leq$ 1.5 x ULN** |
| Serum creatinine | < 1.5x ULN or creatinine clearance (CrCl) > 40 mL/min (measured using |

the Cockcroft-Gault formula below):

$$\text{Female CrCl} = \frac{(140 - \textit{age in years}) * \textit{weight in kg} * 0.85}{72 * \textit{serum creatinine in mg / dL}}$$

$$\text{Male CrCl} = \frac{(140 - \textit{age in years}) * \textit{weight in kg} * 1.00}{72 * \textit{serum creatinine in mg / dL}}$$

* Transfusion to achieve this level is not permitted within 2 weeks of Cycle 1 Day 1 of immunotherapy

** Subjects with Gilbert syndrome may proceed as long as total bilirubin <3.0 mg/dL.

3.3.7 Patients must inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.

3.3.8 Female patient of childbearing potential (WOCBP) (defined below) must have a negative urine or serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]) within 24 hours prior to the start of study treatment). 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. If a patient has a positive serum pregnancy test, then an ultrasound must be done to rule out pregnancy to continue on trial.

- A woman is considered of childbearing potential (WOCBP) following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
- Women in the following categories are not considered WOCBP:
  - Pre-menarchal
  - Pre-menopausal female with one of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy or tubal ligation
    - Documented bilateral oophorectomy
  - Postmenopausal female - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.

3.3.9 WOCBP must be willing to use one of the highly effective methods of contraception (which have a failure rate of < 1% when used consistently and correctly) listed here during study duration and until the end of relevant systemic exposure, starting with Visit 1 through 5 months after the end of study

treatment. Approved contraceptive methods include combined (estrogen- and progestogen-containing) hormonal contraception (oral, intravaginal, transdermal), progestogen-only hormonal contraception (oral, injectable), implantable progestogen-only hormonal contraception, other hormonal methods of contraception (vaginal ring, injectables, implants and intrauterine hormone-releasing system), intrauterine device and bilateral tubal occlusion.

A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant. It is not necessary to use any other method of contraception when complete abstinence is elected. WOCBP participants who choose complete abstinence must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence.

The following are unacceptable methods of contraception:

- Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously
- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal Sponge with spermicide
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action
- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus).
- Spermicide only
- Lactation amenorrhea method (LAM)

3.3.10 Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until end of relevant systemic exposure defined as 7 months after the end of study treatment.

- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 7 months after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 7 months after the end of study treatment.
- Refrain from donating sperm for the duration of the study treatment and until 7 months after the end of study treatment.
- Confirmed azoospermic males are exempt from contraceptive requirements.

## 3.4 Exclusion Criteria for Continuation in Study and Initiation of Immunotherapy

**Prior Therapy**

3.4.1 Any anti-neoplastic biologics, vaccines or hormonal treatment, including investigational drugs, within 28 days of the first dose of study combination immunotherapy administration.

3.4.2 Is currently participating or has participated in a study of an investigational agent or using an investigational device for the treatment of cancer. The patient's participation in other clinical trials must be approved by the Principal Investigator.

3.4.3 Patients receiving active immunosuppressive agents and chronic use of systemic corticosteroids within 14 days of the first dose of study combination immunotherapy administration.

3.4.4 Patients who have received a live vaccine within 28 days of the first dose of study immunotherapy administration. Examples of live vaccine 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.

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

**Medical History and Concurrent Diseases**

3.4.6 Any evidence of metastatic disease by radiologic imaging

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

3.4.8 Requires the use of home oxygen.

3.4.9 Uncontrolled or significant cardiovascular disease including, but not limited to, any of the following:

- Myocardial infarction or stroke/transient ischemic attack within the past 6 months
- Uncontrolled angina within the past 3 months
- Any history of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes)
- History of other clinically significant heart disease (e.g., cardiomyopathy, congestive heart failure with New York Heart Association functional classification III-IV, pericarditis, significant pericardial effusion, or myocarditis)
- Cardiovascular disease-related requirement for daily supplemental oxygen therapy

3.4.10 Evidence of uncontrolled, active infection, requiring parenteral anti-bacterial, anti-viral or anti-fungal therapy < 7 days prior to administration of study immunotherapy treatment.

3.4.11 Other uncontrolled intercurrent illness including, but not limited to, chronic ongoing infection or psychiatric illness/social situations that would limit compliance with study requirements.

3.4.12 Current or recent (within 3 months of study treatment administration) gastrointestinal disease that could impact the absorption of study treatment.

3.4.13 Any gastrointestinal surgery that is likely impact upon the absorption of study treatment.

3.4.14 Inability to be venipunctured and/or tolerate venous access.

3.4.15 Patients who have had surgery within 28 days of the first dose of study combination immunotherapy administration, excluding minor procedures (dental work, skin biopsy, etc.), duodenal stent placement, celiac plexus block, vascular access devices and biliary stent placement. Participants must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before the first dose of study immunotherapy treatment.

**Restricted Concomitant Therapy**

3.4.16 Current or prior use of strong/moderate CYP3A4 inhibitors or inducers within 28 days or 5 half-lives, whichever is shorter, prior to the first dose of BMS-813160. (See **Appendix C**).

3.4.17 Current or prior use of Class I antiarrhythmics (eg, quinidine, procainamide, disopyramide, lidocaine, phenytoin, mexiletine, tocainide, flecainide, propafenone, and moricizine) within 28 days of the first dose of BMS-813160.

3.4.18 Current use of tricyclic antidepressants.

**Physical and Laboratory Test Findings**

3.4.19 Ascites needing paracentesis or medical management.

3.4.20 Any of the following on 12-lead electrocardiogram (ECG) prior to study treatment administration, confirmed by repeat.

- QRS ≥ 120 msec, except right bundle branch block
- QTcF (QT corrected for heart rate using Fridericia's method) ≥ 480 msec, except right bundle branch block

**Allergies and Adverse Drug Reaction**

3.4.21 History of severe hypersensitivity reaction to any monoclonal antibody.

3.4.22 History of allergy to study treatments or any of its components of the study arm that participant is enrolling.

3.4.23 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.

**Other Exclusion Criteria**

3.4.24 Women who are pregnant or breastfeeding.

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

## 3.5 Eligibility Criteria for Post-surgical Immunotherapy

Patients must have eligibility checked prior to receiving post-surgical immunotherapy, and must meet the following criteria for continued participation in the study. Patients who are deemed unresectable due to local progression (i.e. without metastatic disease) may continue directly to Cycle 2 immunotherapy without rescreening. No eligibility checklist is necessary for these patients.

3.5.1 ECOG performance status 0-1 (**Appendix A**).

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

| | |
|---|---|
| White blood cell count | $\geq$ 2,000 cells/mm$^3$ |
| Absolute lymphocyte count | $\geq$ 500 cells/mm$^3$ |
| Absolute neutrophil count | $\geq$ 1,000 cells/mm$^3$ |
| Hemoglobin | $\geq$ 8 g/dL* |
| Platelets | $\geq$ 80,000 cells/mm$^3$* |
| AST and ALT | $\leq$ 3 x ULN |
| Total bilirubin | $\leq$ 1.5 x ULN** |
| Serum creatinine | < 1.5x ULN or creatinine clearance (CrCl) > 40 mL/min (measured using the Cockcroft-Gault formula below): |

$$\text{Female CrCl} = \frac{(140 - \textit{age in years}) * \textit{weight in kg} * 0.85}{72 * \textit{serum creatinine in mg / dL}}$$

$$\text{Male CrCl} = \frac{(140 - \textit{age in years}) * \textit{weight in kg} * 1.00}{72 * \textit{serum creatinine in mg / dL}}$$

* Transfusion to achieve this level is not permitted within 2 weeks of Cycle 2 Day 1 of immunotherapy

** Subjects with Gilbert syndrome may proceed as long as total bilirubin <3.0 mg/dL.

3.5.3 Patients must inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.

3.5.4 Female patient of childbearing potential (WOCBP) (defined below) must have a negative urine or serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]) within 24 hours prior to the start of study treatment). 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. If a patient has a positive serum pregnancy test, then an ultrasound must be done to rule out pregnancy to continue on trial.

- A woman is considered of childbearing potential (WOCBP) following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
- Women in the following categories are not considered WOCBP:
  - Pre-menarchal
  - Pre-menopausal female with one of the following:

    - Documented hysterectomy
    - Documented bilateral salpingectomy or tubal ligation
    - Documented bilateral oophorectomy
- Postmenopausal female - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.

3.5.5 WOCBP must be willing to use one of the highly effective methods of contraception (which have a failure rate of < 1% when used consistently and correctly) listed here during study duration and until the end of relevant systemic exposure, starting with Visit 1 through 5 months after the end of study treatment. Approved contraceptive methods include combined (estrogen- and progestogen-containing) hormonal contraception (oral, intravaginal, transdermal), progestogen-only hormonal contraception (oral, injectable), implantable progestogen-only hormonal contraception, other hormonal methods of contraception (vaginal ring, injectables, implants and intrauterine hormone-releasing system), intrauterine device and bilateral tubal occlusion.

A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant. It is not necessary to use any other method of contraception when complete abstinence is elected. WOCBP participants who choose complete abstinence must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence.

The following are unacceptable methods of contraception:

- Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously
- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal Sponge with spermicide
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action
- Periodic abstinence (calendar, symptothermal, post-ovulation methods)

- Withdrawal (coitus interruptus).
- Spermicide only
- Lactation amenorrhea method (LAM)

3.5.6 Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until end of relevant systemic exposure defined as 7 months after the end of study treatment.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 7 months after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 7 months after the end of study treatment.
- Refrain from donating sperm for the duration of the study treatment and until 7 months after the end of study treatment.
- Confirmed azoospermic males are exempt from contraceptive requirements.

## 3.6 Exclusion Criteria for Post-surgical Immunotherapy

Patients who are deemed unresectable due to local progression (i.e. without metastatic disease) may continue directly to Cycle 2 immunotherapy without rescreening. No eligibility checklist is necessary for these patients.

### Prior Therapy

3.6.1 Any anti-neoplastic biologics, vaccines or hormonal treatment, including investigational drugs, within 28 days of the first dose of study combination immunotherapy administration.

3.6.2 Patients with a history of past treatment with immunotherapy agents prior to initial enrollment into this study (including, but not limited to: IL-2, interferon, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-OX-40, anti-CD40, anti-CTLA-4 or anti-CCR2/5 antibodies).

3.6.3 Is currently participating or has participated in a study of an investigational agent or using an investigational device for the treatment of cancer. The patient's participation in other clinical trials must be approved by the Principal

Investigator.

3.6.4 Patients receiving active immunosuppressive agents and chronic use of systemic corticosteroids within 14 days of the first dose of study combination immunotherapy administration.

3.6.5 Patients who have received a live vaccine within 28 days of the first dose of study immunotherapy administration. Examples of live vaccine 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.

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

**Medical History and Concurrent Diseases**

3.6.7 Any evidence of metastatic disease by radiologic imaging

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

3.6.9 Requires the use of home oxygen.

3.6.10 Uncontrolled or significant cardiovascular disease including, but not limited to, any of the following:

- Myocardial infarction or stroke/transient ischemic attack within the past 6 months
- Uncontrolled angina within the past 3 months
- Any history of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes)
- History of other clinically significant heart disease (eg, cardiomyopathy, congestive heart failure with New York Heart Association functional classification III-IV, pericarditis, significant pericardial effusion, or myocarditis)
- Cardiovascular disease-related requirement for daily supplemental oxygen therapy

3.6.11 Evidence of uncontrolled, active infection, requiring parenteral anti-bacterial,

anti-viral or anti-fungal therapy < 7 days prior to administration of study immunotherapy treatment.

3.6.12 Other uncontrolled intercurrent illness including, but not limited to, chronic ongoing infection or psychiatric illness/social situations that would limit compliance with study requirements.

3.6.13 Current or recent (within 3 months of study treatment administration) gastrointestinal disease that could impact the absorption of study treatment.

3.6.14 Any gastrointestinal surgery that is likely impact upon the absorption of study treatment.

3.6.15 Inability to be venipunctured and/or tolerate venous access.

3.6.16 Patients who have had surgery within 28 days of the first dose of study combination immunotherapy administration, excluding minor procedures (dental work, skin biopsy, etc.), duodenal stent placement, celiac plexus block, vascular access devices and biliary stent placement. Participants must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before the first dose of study immunotherapy treatment.

**Restricted Concomitant Therapy**

3.6.17 Current or prior use of strong/moderate CYP3A4 inhibitors or inducers within 28 days or 5 half-lives, whichever is shorter, prior to the first dose of BMS-813160. (See **Appendix C**).

3.6.18 Current or prior use of Class I antiarrhythmics (eg, quinidine, procainamide, disopyramide, lidocaine, phenytoin, mexiletine, tocainide, flecainide, propafenone, and moricizine) within 28 days of the first dose of BMS-813160.

3.6.19 Current use of tricyclic antidepressants

**Physical and Laboratory Test Findings**

3.6.20 Ascites needing paracentesis or medical management.

3.6.21 Any of the following on 12-lead electrocardiogram (ECG) prior to study treatment administration, confirmed by repeat.

- QRS ≥ 120 msec, except right bundle branch block
- QTcF (QT corrected for heart rate using Fridericia's method) ≥ 480 msec, except right bundle branch block

**Allergies and Adverse Drug Reaction**

3.6.22 History of severe hypersensitivity reaction to any monoclonal antibody.

3.6.23 History of allergy to study treatments or any of its components of the study arm that participant is enrolling.

3.6.24 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.

**Other Exclusion Criteria**

3.6.25 Women who are pregnant or breastfeeding.

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

## 3.7 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 5.1**. Enrolled patients will receive eight to sixteen 14-day cycles of FOLFIRINOX-based chemotherapy (i.e. FOLFIRINOX, 5-FU/leucovorin, FOLFIRI) and SBRT (6.6. Gy x 5 days). SBRT will be initiated between two to four weeks after completion of chemotherapy. Both chemotherapy and SBRT are considered standard of care. If patients remain eligible for continuation in the study, they will receive one 28-day cycle of combination immunotherapy within two weeks of completion of SBRT.

Due to availability of BMS-813160, study enrollment was closed as of December 19, 2022. Patients randomized prior to this will continue receiving study treatment as planned until drug supply expires on July 31, 2023, then will continue to receive any remaining study cycles without BMS-813160. Patients who were enrolled but not randomized prior to December 19, 2022 (i.e. those receiving chemotherapy) will be assigned to a new arm (Arm C.

In phase I, the combination immunotherapy consists of nivolumab, CCR2/CCR5 dual-antagonist (BMS-813160) and GVAX. In phase II, the first 10 patients (those randomized before December 19, 2022) will be randomized 1:1 between Arm A and Arm B. Remaining patients will be assigned to Arm C. Arm A will receive nivolumab and BMS-813160, and Arm B will receive nivolumab, BMS-813160 and GVAX. Arm C patients will receive nivolumab and BMS-813160 for Cycle 1 (prior to surgery) and then nivolumab and GVAX for Cycles 2 and beyond. Due to the span of time between enrollment and study drug administration (approximately 5-9 months of chemotherapy and SBRT), it is possible we will not know whether to enroll several patients to Phase I or Phase II at the time of their consent. Until a sufficient number of patients have completed their first cycle of study treatment in Phase I to allow us to determine the Phase II dose of BMS-813160, we will inform new study candidates of both possibilities during consent. These patients will sign an informed consent that describes both Phase I and Phase II at the time of enrollment (prior to SOC chemotherapy) and will be informed of their specific phase and sign either a Phase I or Phase II consent form prior to starting study treatment.

Surgery will be scheduled to occur between five to seven weeks after completion of SBRT. Surgery is considered standard of care and only toxicities considered related to study procedures or treatment will be collected from the time of surgery until the start of Cycle 2. If the surgery is scheduled to be after the completion of the 28-day Cycle 1 of combination immunotherapy, anti-CCR2/5 therapy will be continued up to the day before surgery (but a second dose of nivolumab and GVAX will not be administered because this is not considered a new cycle). If the patient is not a surgical candidate, they will undergo an EUS-guided tumor biopsy. Both surgically-resected and non-surgical candidates who are eligible for continuation in the study post-surgical evaluation will continue to receive 4 more 28-day cycles of their assigned combination immunotherapy or till development of metastatic disease.

For those who undergo a surgery or NanoKnife procedure, immunotherapy will be initiated 6 to 12 weeks after the procedure. For those who are not surgical candidates, the immunotherapy will not be held.

Patients who remain free of metastatic disease at the completion of 5 cycles of combined immunotherapy (1 cycle prior to surgery and 4 cycles post-surgical evaluation) will be eligible to enroll in the optional **Maintenance Treatment Phase.** During the 24-week maintenance phase, Phase I and Arm B patients will receive BMS-813160 daily, nivolumab every four weeks, and GVAX once, Arm A patients will receive BMS-813160 daily and nivolumab every four weeks, and Arm C patients will receive nivolumab every four weeks and GVAX once.

**Table 1: Study Regimen**

| ***Agent*** | ***Pre-medications, Precautions*** | ***Dose*** | ***Route*** |
|---|---|---|---|
| GVAX<br>*(Cycle 1: Phase 1 and Arm B Cycles 2+: Phase 1, Arm B, and Arm C patients)* | EMLA cream (approximately 2.5 g/site at least 1 hour prior to vaccination) | $5x10^8$ cells | Six intradermal injections every 4 weeks |
| Nivolumab<br>*(All patients)* | No prophylactic pre-medications unless indicated by previous experience in an individual subject | 480 mg | IV over 30 minutes every 4 weeks* |
| CCR2/CCR5 dual-antagonist (BMS-813160)<br>*(Cycle 1: all patients Cycles 2+: Phase 1, Arm A, and Arm B patients)* | No prophylactic pre-medications unless indicated by previous experience in an individual subject | Dose Level 1 (Phase1): 150 mg<br><br>Dose Level 2 (Phase 1): 300 mg<br><br>Phase 2 dose: 300 mg | PO twice a day** |

*Infusion times are approximate (+25 /- 10 min) and may need to be adjusted based on subject tolerability.
**At least 8 hours is recommended between doses of BMS-813160.

Please see **Section 5.1** for guidance regarding dosing delays.

### 4.1.1 GM-CSF Vaccine

The vaccine consists of equal numbers ($2.5 \times 10^8$ each) of Panc 6.03pcDNA1GM-CSF and Panc 10.05 pcDNA1GM-CSF combined into a single vaccination. Each of the vaccine components consists of a cultured, irradiated, allogeneic pancreatic tumor cell line that has been genetically modified with a plasmid vector encoding the cDNA for human GM-CSF. The final vaccine population secretes approximately 80-100 ng/ $10^6$ cells/ 24 hours of GM-CSF. Vaccine cells from each pancreas tumor cell line frozen at $1.25 \times 10^8$ cells/vial (2 vials per cell line) in an injectable formulation of Hespan (6%

Hetastarch in 0.9% sodium chloride with 2% human serum albumin and 5% DMSO) will be thawed on the day of vaccination and taken up into syringes. Each vaccination will consist of six total intradermal injections, two each in the right and left thighs, and two in the non-dominant arm. In the event that the specified limb is contraindicated, the dominant arm may be used**.** A lidocaine-based topical anesthetic cream will be applied to the injection site at least 1 hour prior to vaccination to diminish the discomfort associated with intradermal injections.

### 4.1.2 **Anti-PD-1 Therapeutic Antibody Nivolumab (Opdivo®, BMS-936558)**

Nivolumab 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. The nivolumab dose that will be used in this study is 480 mg flat dose administered as an intravenous infusion over 30 minutes every 4 weeks. Antiemetic medications should not be routinely administered prior to dosing except as indicated by patient's prior reaction.

### 4.1.3 **CCR2/CCR5 dual-antagonist (BMS-813160)**

BMS-813160 is an equipotent and reversible small-molecule dual antagonist of CCR2 and CCR5, and potently inhibits CCR2- and CCR5-dependent functions in response to all known ligands.

Multiple doses of BMS-813160 [10 to 300 mg daily (N=24) and 300 to 900 mg BID (N=18) for 14 days] were safe and generally well tolerated in healthy participants, with no deaths, serious adverse events (SAEs) or discontinuations due to adverse events (AEs).[40] There was no apparent dose relationship with respect to AEs. All AEs were considered to be mild in intensity, except for one participant who had a headache of moderate intensity while receiving BMS-813160 10 mg QD. There were concentration-dependent increases in QRS and PR intervals and HR at 600 mg BID and 900 mg BID, without any ECG-related AEs or clinical sequelae. The increases in PR (mean < 16 msec at peak), QRS (mean < ~10 msec at peak), and HR (< ~10 bpm at peak) were not considered clinically significant. Concentration-response assessment showed no QTc prolongation.

BMS-813160 was generally safe and well tolerated when administered for 12 weeks to participants with diabetic kidney disease (DKD); 88 participants received BMS-813160 150 mg daily (N = 29), BMS-813160 300 mg BID (N = 30), or placebo (N = 29).[42] The majority of AEs were mild or moderate in severity. There were no marked differences in AE frequencies in participants receiving BMS-813160 (any dose) compared with placebo, and no dose-related trends were apparent in the frequency of any AEs. The most frequently reported AEs were edema peripheral (6.8% of subjects), fatigue (5.7% of subjects), diarrhea (3.4% of subjects), back pain (3.4% of subjects), and headache (3.4% of subjects).

BMS-813160 at doses ≥ 300 mg BID results in sustained inhibition of CCR2 and CCR5 on day 14, and was safe and well tolerated in both healthy participants and patients with DKD. The combination of nivolumab, GVAX and BMS-813160 may cause more immune-mediated adverse events than when each therapy is given alone. For this reason, in this study, we will have two dose levels: 150 mg PO BID for dose level 1 and 300 mg PO BID for dose level 2.

BMS-813160 is cleared by metabolism, direct urinary and biliary/fecal excretion. The metabolism of BMS-813160 is primarily mediated via cytochrome P450 3A4, with some contribution from CYP3A5, and is also a substrate for P-glycoprotein (P-gp). Hence, there is potential for drug-drug interactions if BMS-813160 is co-administered with inhibitors or inducers of CYP3A or P-gp. BMS-813160 is not expected to alter the clearance of compounds that are CYP, UGT, or P-gp substrates. However, BMS-813160 and its prominent metabolite, BMS-939429, inhibited MATE1. See **Section 4.3** for restrictions on co-medications.

## 4.2 General Concomitant Medication and Supportive Care Guidelines

### 4.2.1 GVAX Pancreas Vaccine

Local skin reactions at vaccine sites may be treated with cold packs, 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.

### 4.2.2 Nivolumab

Nivolumab is a fully humanized monoclonal antibody. 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.

#### 4.2.2.1 Infusion Reactions

Infusion reactions, including high-grade hypersensitivity reactions, following administration of nivolumab are uncommon. 6.4% (127/1994) and 2.5% (10/407) had infusion reactions when nivolumab was given as a single agent and in combination with ipilimumab, respectively. Severe infusion reactions have been reported in less than 1.0% of patients in clinical trials. Infusion reactions may

consist of fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty in breathing during and immediately after administration of nivolumab.

Discontinue nivolumab for severe and life-threatening infusion reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions.

Patients should be closely monitored for such reactions. Guidelines for patients who experience an infusion related or allergic reaction during or after infusion with nivolumab are shown below.

**Table 2: Guidance on Infusion and Hypersensitivity Reactions**

| NCI CTCAE Grade | Treatment | Premedication at subsequent dosing |
|---|---|---|
| Grade 1<br>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<br>Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hours | **Stop Infusion and monitor symptoms.**<br>Additional appropriate medical therapy may include but is not limited to:<br>IV fluids, Antihistamines, NSAIDS, Acetaminophen, Narcotics<br>Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.<br>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 pre-medicated for the next scheduled dose. | Subject may be pre-medicated 1.5h (± 30 minutes) prior to infusion of nivolumab with:<br>Diphenhydramine 50 mg PO (or equivalent dose of antihistamine).<br>Acetaminophen 500-1000 mg PO (or equivalent dose of antipyretic). |
| Grade 3<br>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) | **Stop Infusion and monitor symptoms.**<br>Additional appropriate medical therapy may include but is not limited to:<br>IV fluids, Antihistamines, NSAIDS, Acetaminophen, Narcotics, Oxygen, Vasopressors, Corticosteroids, Epinephrine<br>Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.<br>Hospitalization may be indicated.<br>**Subject is permanently discontinued from further trial treatment administration if the Grade 3 infusion reaction does not return to Grade 1 in less than 6 hours or if the subject requires vasopressors or epinephrine.** | Subject may be pre-medicated 1.5h (± 30 minutes) prior to infusion of nivolumab with:<br>Diphenhydramine 50 mg PO (or equivalent dose of antihistamine).<br>Acetaminophen 500-1000 mg PO (or equivalent dose of antipyretic). |

| NCI CTCAE Grade | Treatment | Premedication at subsequent dosing |
|---|---|---|
| Grade 4:<br>Life-threatening; pressor or ventilatory support indicated | **Stop Infusion and monitor symptoms.**<br>Additional appropriate medical therapy may include but is not limited to:<br>IV fluids, Antihistamines, NSAIDS, Acetaminophen, Narcotics, Oxygen, Pressors, Corticosteroids, Epinephrine<br>Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.<br>Hospitalization is indicated.<br>**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. | | |

#### 4.2.2.2 **Immune-Related Adverse Events (IRAEs)**

Blocking PD-1 and CCR2/5 functions may permit the emergence of auto-reactive T-cells and resultant clinical autoimmunity. IRAE may occur in the following categories: gastrointestinal, renal pulmonary, hepatic, endocrinopathies, skin and neurological.

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 Case Report Form (CRF).

### 4.3 Prohibited and Restricted Therapies

Medications taken within 4 weeks prior to study treatment administration must be recorded.

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

- In vitro, the metabolism of BMS-813160 was primarily mediated via cytochrome P450 (CYP) 3A4, with some contribution from CYP3A5, and BMS-813160 was also a substrate for P-glycoprotein (P-gp). Based on these results, the potential exists for drug-drug interactions if BMS-813160 is co-administered with inhibitors or inducers of CYP3A or P-gp. Therefore use of any strong inhibitors or inducers of CYP3A4 or P-gp is not allowed (see **Appendix C**).
- Grapefruit and Seville oranges and their juices can inhibit CYP3A4 and should not be consumed while on study.

- Class I antiarrhythmics (eg, quinidine, procainamide, disopyramide, lidocaine, phenytoin, mexiletine, tocainide, flecainide, propafenone, moricizine).
- 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, anti-CCR2/5 or anti-CTLA-4 antibodies.
- Systemically active steroids can be used, but should be reported to the Principal Investigator, BMS and IND Sponsor. Steroid treatment courses that are longer than 4 days should be completed at least 14 days prior to resuming study-related treatments (See **Section 5.1** for dosing delays for steroids).
- Immunosuppressive agents.
- Filgrastim (Neupogen® or G-CSF), sargramostim (Leukine® or GM-CSF), erythropoietin, other growth factors.
- Live vaccines (examples of live vaccines include, but are not limited to: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid [oral] vaccine). 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.
- Tricyclic antidepressants

4.3.2 Caution is warranted in the following situations:

- Caution is warranted with concomitant use of MATE1 substrates with a narrow therapeutic index.
- Caution is warranted when administering BMS-813160 to participants taking drugs that are moderate inhibitors or inducers of CYP3A4. Moderate CYP3A4 modulators (i.e. inhibitor or inducer) are allowed with caution only after the first 4 weeks of receiving combination immunotherapy. See **Appendix C** for a list of CYP3A4 modulators.
- Methadone (in particular at high doses) due to potential sodium channel blockade

## 4.4 Definition of an Overdose for this Protocol

No cases of overdose have been reported in clinical trials for BMS-813160, nor GVAX pancreas vaccine. In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted immediately. There are no specific antidotes for nivolumab, BMS-813160 nor GVAX pancreas vaccine.

An overdose is defined as the accidental or intentional administration of any dose greater than the assigned dose of study treatment that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see **Section 6.5).**

In the event of an overdose, the Principal Investigator will do the following:

- Contact BMS Worldwide Safety [redacted] and IND Sponsor immediately using the SAE Reporting Form in Appendix B.
- Closely monitor the participant for AEs/SAEs and laboratory abnormalities until effects can no longer be detected systemically
- Obtain a plasma sample for PK analysis if requested by BMS or IND Sponsor, or if deemed necessary by the Principal Investigator (determined on a case-by-case basis)
- Document the quantity of the excess dose as well as the duration of the overdosing in the Case Report Form (CRF)

Decisions regarding dose interruptions or modifications will be made by the Principal Investigator in consultation with BMS and/or the IND Sponsor based on the clinical evaluation of the participant.

## 4.5 Contraception, Use in Pregnancy, Use in Nursing

### 4.5.1 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 [postmenopausal is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes; women under the age of 55 years must have a serum follicle stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause], or
3) not heterosexually active for the duration of the study, or
4) heterosexually active and willing to use 2 methods of birth control (which is

also required for the female partners of male patients).

Women of childbearing potential must use one of the highly effective methods of contraception (which have a failure rate of < 1% when used consistently and correctly) listed here during study duration and until the end of relevant systemic exposure, starting with Visit 1 through 5 months after the end of study treatment. Approved contraceptive methods include combined (estrogen- and progestogen-containing) hormonal contraception (oral, intravaginal, transdermal), progestogen-only hormonal contraception (oral, injectable), implantable progestogen-only hormonal contraception, other hormonal methods of contraception (vaginal ring, injectables, implants and intrauterine hormone-releasing system), intrauterine device and bilateral tubal occlusion.

A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant. It is not necessary to use any other method of contraception when complete abstinence is elected. WOCBP participants who choose complete abstinence must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence.

The following are unacceptable methods of contraception:

- Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously
- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal Sponge with spermicide
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action
- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus).
- Spermicide only
- Lactation amenorrhea method (LAM)

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure:

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until end of relevant systemic exposure defined as 7 months after the end of study treatment.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 7 months after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 7 months after the end of study treatment.
- Refrain from donating sperm for the duration of the study treatment and until 7 months after the end of study treatment.
- Confirmed azoospermic males are exempt from contraceptive requirements.

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.

### 4.5.2 **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 or may have been pregnant at the time of investigational product exposure, including during at least 5 half-lives after study drug administration, the patient will immediately be removed from the study. The IND Sponsor and [redacted] will be notified immediately via either the CIOMS, MedWatch or appropriate Pregnancy Surveillance Form in accordance with SAE reporting procedures. Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

The study site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information will be reported on the CIOMS, MedWatch, BMS Pregnancy Surveillance Form, or approved site SAE form. A BMS Pregnancy Surveillance Form may be provided to the study site upon request. The outcome of the pregnancy will also be reported to the IND Sponsor.

The outcome must be reported to the IND Sponsor within 24 hours [redacted] 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).

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form. In order for BMS, IND Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information.

#### 4.5.3 **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.

### 4.6 Dose Limiting Toxicity

Dose limiting toxicities (DLTs) will be defined based on the incidence, duration and grade of AEs for which no alternate cause can be identified. Adverse events will be evaluated according to the NCI CTCAE v5.0. Every attempt must be made to assign relationship to BMS-813160, nivolumab and/or GVAX. Also, to meet criteria for dose limiting, AEs have to be related to study treatment, not be related to disease progression, be clinically relevant, and be a clinically relevant shift from baseline. DLTs will be assessed in the first cycle of Phase I (starting Cycle 1 Day 1 through prior to initiation of Cycle 2).

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.

Dose limiting toxicities can include the following AEs (meeting the preceding criteria):

1) **Hepatic DLT**
   a) Any ≥ Grade 3 elevation of AST, ALT, or total bilirubin
   b) Grade 2 AST or ALT with symptomatic liver inflammation (e.g. right upper quadrant tenderness, jaundice, pruritus)
   c) Potential drug induced liver injury (DILI), which is defined as:
      i. AST or ALT > 3x ULN
         AND
      ii. Concurrent total bilirubin > 2x ULN without initial findings of cholestasis (elevated serum alkaline phosphatase, e.g. findings

consistent with Hy's law or FDA definition of potential drug-induced liver injury [DILI]) (Note that this special category of DLT uses ULN rather than Common Toxicity Criteria Grade for definition.)

AND

iii. No other immediately apparent possible causes of transaminase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre- existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

**2) Hematologic DLT**

a) Grade 4 neutropenia ≥ 7 days in duration
b) Grade 4 lymphopenia ≥ 7 days in duration
c) Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding, or any requirement for platelet transfusion
d) Grade ≥ 3 febrile neutropenia
e) Grade ≥ 3 hemolysis (i.e. requiring transfusion or medical intervention such as steroids)
f) Grade 4 anemia not explained by underlying disease

**3) Nonhepatic Nonhematologic DLT**

a) Grade 2 or greater episcleritis, uveitis, or iritis
b) Any other Grade 2 eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks OR requires systemic treatment
c) Grade 2 myocarditis
d) Grade 3 pneumonitis, bronchospasm, or neurologic toxicity requires discontinuation
e) Any Grade 3 or greater nondermatologic, nonhepatic, nonhematologic toxicity will be considered a DLT with the following specific EXCEPTIONS:
   i. Grade 3 electrolyte or laboratory abnormalities that are not complicated by associated clinical adverse experiences, last less than 48 hours and either resolve spontaneously or respond to conventional medical intervention
   ii. Grade 3 or 4 elevation of amylase or lipase not associated with clinical or radiographic evidence of pancreatitis
   iii. Grade 3 nausea, vomiting, or diarrhea that lasts less than 48 hours and either resolves spontaneously or responds to conventional medical intervention
   iv. Isolated Grade 3 fever not associated with hemodynamic compromise (e.g. hypotension, clinical or laboratory evidence of impaired end-organ perfusion)
   v. Grade 3 endocrinopathy that is well-controlled by hormone replacement
   vi. Grade 3 tumor flare (defined as pain, irritation, or rash that localizes to site of known or suspected tumor)

vii. Grade 3 fatigue
viii. Grade 3 infusion reaction that returns to Grade 1 in less than 6 hours as long as vasopressors or epinephrine were not required

**4) Dermatologic DLT**

a) Grade 3 rash if no improvement (ie, resolution to ≤ Grade 1) after a 1- to 2-week dosing delay
b) Grade 4 rash of any duration

## 4.7 Unacceptable Toxicities

Unacceptable toxicities will be used to monitor safety from Cycle 2 Day 1 of Phase I through to end of study treatment and from Cycle 1 Day 1 of Phase II through to end of treatment (see **Section 4.8** for stopping rules). Adverse events will be evaluated according to the NCI CTCAE v5.0.

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.

Unacceptable toxicities are defined as:

1) Treatment-related ≥ grade 4 AEs; however, an EXCEPTION may be made for the following upon consultation between the Principal Investigator, IND Sponsor and BMS:
   a) Grade 4 electrolyte abnormalities < 72 hours in duration
   b) Grade 4 neutropenia < 7 days in duration
   c) Grade 4 lymphopenia < 7 days in duration
   d) Grade 4 increase in amylase or lipase that is not associated with clinical or radiographic evidence of pancreatitis
   e) Grade 4 hyperglycemia where symptoms are controlled on hormone replacement therapy
2) Treatment-related grade 3 AEs, EXCEPT:
   a) Grade 3 electrolyte or laboratory abnormalities that are not complicated by associated clinical adverse experiences, last less than 48 hours and either resolve spontaneously or respond to conventional medical intervention
   b) Grade 3 elevation of amylase or lipase not associated with clinical or radiographic evidence of pancreatitis
   c) Grade 3 nausea, vomiting, or diarrhea that lasts less than 48 hours and either resolves spontaneously or responds to conventional medical intervention
   d) Grade 3 thrombocytopenia WITHOUT bleeding, or any requirement for platelet transfusion
   e) Isolated Grade 3 fever not associated with hemodynamic compromise (e.g. hypotension, clinical or laboratory evidence of impaired end-organ perfusion)
   f) Grade 3 endocrinopathy that is well-controlled by hormone replacement

g) Grade 3 tumor flare (defined as pain, irritation, or rash that localizes to site of known or suspected tumor)
h) Grade 3 fatigue
i) Grade 3 infusion reaction that returns to Grade 1 in less than 6 hours as long as vasopressors or epinephrine were not required
j) Grade 3 dermatologic AEs that improves (i.e., resolution to ≤ Grade 1) after a 1- to 2-week dosing delay.

3) Grade 2 or greater episcleritis, uveitis, or iritis
4) Any other Grade 2 eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks OR requires systemic treatment
5) Potential DILI (defined in **section 4.6**)

### 4.8 Stopping Rules

We will be monitoring toxicity for each arm in the Phase II portion, and if we observe >33% unacceptable toxicities in any arm, we will halt the enrollment pending safety evaluations and consideration by Principal Investigator, IND Sponsor, BMS and Medical Expert Committee (MEC).

### 4.9 Criteria for Removal from Study Treatment

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

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, or
- Patient is lost to follow-up.

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:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent for treatment,
- Development of distant metastatic disease,
- Intercurrent illness that prevents further administration of treatment,
- Dose-limiting toxicities with exceptions to treatment discontinuation as described in **Section 4.6**,
- Fulfilling criteria for permanent discontinuation of BMS-813160 (see **Section 5.2.6.2**),

- Unacceptable toxicity/toxicities with exceptions to treatment discontinuation as described in **Section 4.7**,
- Need for >2 dose delays due to the same toxicity as per the dose delay guidelines (see **Section 5.1**),
- If any one or more of the study drugs (nivolumab, BMS-813160 and/or GVAX) are discontinued,
- Inability to reduce corticosteroid dose for immune-related adverse reactions to ≤10 mg prednisone or equivalent per day,
- Any dosing delay lasting > 28 days will be cause for permanent discontinuation. Extensions to the period of dose delays may be granted for individual participants on a case-by-case basis after specific consultation and agreement between Principal Investigator, IND Sponsor and BMS in settings where benefit/risk may justify continued study treatment (e.g. participant deriving clinical benefit who requires prolonged steroid taper for management of non-DLT immune-related AEs or experiences delays for management of a non-drug-related AE).
    - Accordingly, dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed. Additionally, dosing delays > 28 days that occur for non-drug-related reasons may be allowed if approved by the Principal Investigator, IND Sponsor, and BMS.
    - Prior to re-initiating treatment in a participant with a dosing delay lasting > 28 days, the Principal Investigator, IND Sponsor and BMS must be consulted.
    - Tumor assessments should continue as per protocol even if dosing is delayed.
- Investigator's decision to withdraw the subject (the IND Sponsor and BMS should be included in this decision),
- 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 IND Sponsor should be included in this decision,
- Noncompliance with trial treatment or procedure requirements,
- Patient is lost to follow-up, or
- Patient becomes pregnant.

### 4.10 End of Treatment (EOT)

All subjects will return to the study site 30 days (± 7 days) after the last dose of study drug (or within 7 days prior to initiation of a new anti-cancer treatment, whichever comes first) for an EOT evaluation. Procedures and assessments performed at this visit and beyond should follow the respective guidelines described in **Sections 4.11 and 9** as appropriate.

### 4.11 Duration of Follow-up

#### 4.11.1 Safety Follow-up

Subjects who discontinue treatment should be contacted by telephone or email at 100 days (+ 14-day reporting window) from their last dose of study drug or within 7 days before initiation of a new antineoplastic treatment (whichever comes first) to assess for treatment related toxicities. In addition, all SAEs occurring during this time should be reported as well.

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.

#### 4.11.2 Clinical Follow-up

All enrolled subjects who discontinue treatment without disease progression will enter the clinical follow-up portion of the trial. Subjects will begin the clinical follow-up period after they complete the EOT visit. Clinical follow-up visits will occur every 12 weeks (± 2 weeks) until: 1) start of a new antineoplastic therapy (information of the new cancer therapy will be collected), 2) disease progression, 3) death, 4) withdrawal of consent, or 5) study closure, whichever occurs first. Refer to **Section 9** for the schedule of assessments that should be performed at each visit. After disease progression or start of a new antineoplastic therapy, subjects will enter the survival follow-up portion of the trial (**Section 4.11.3**).

#### 4.11.3 Survival Follow-up

Subjects who discontinue treatment and have disease progression or start a new antineoplastic therapy will enter the survival follow-up portion of the trial. Subjects should be contacted every 12 weeks (± 2 weeks) to monitor overall survival. Information of other cancer therapies after discontinuation from the study treatment will be collected as well.

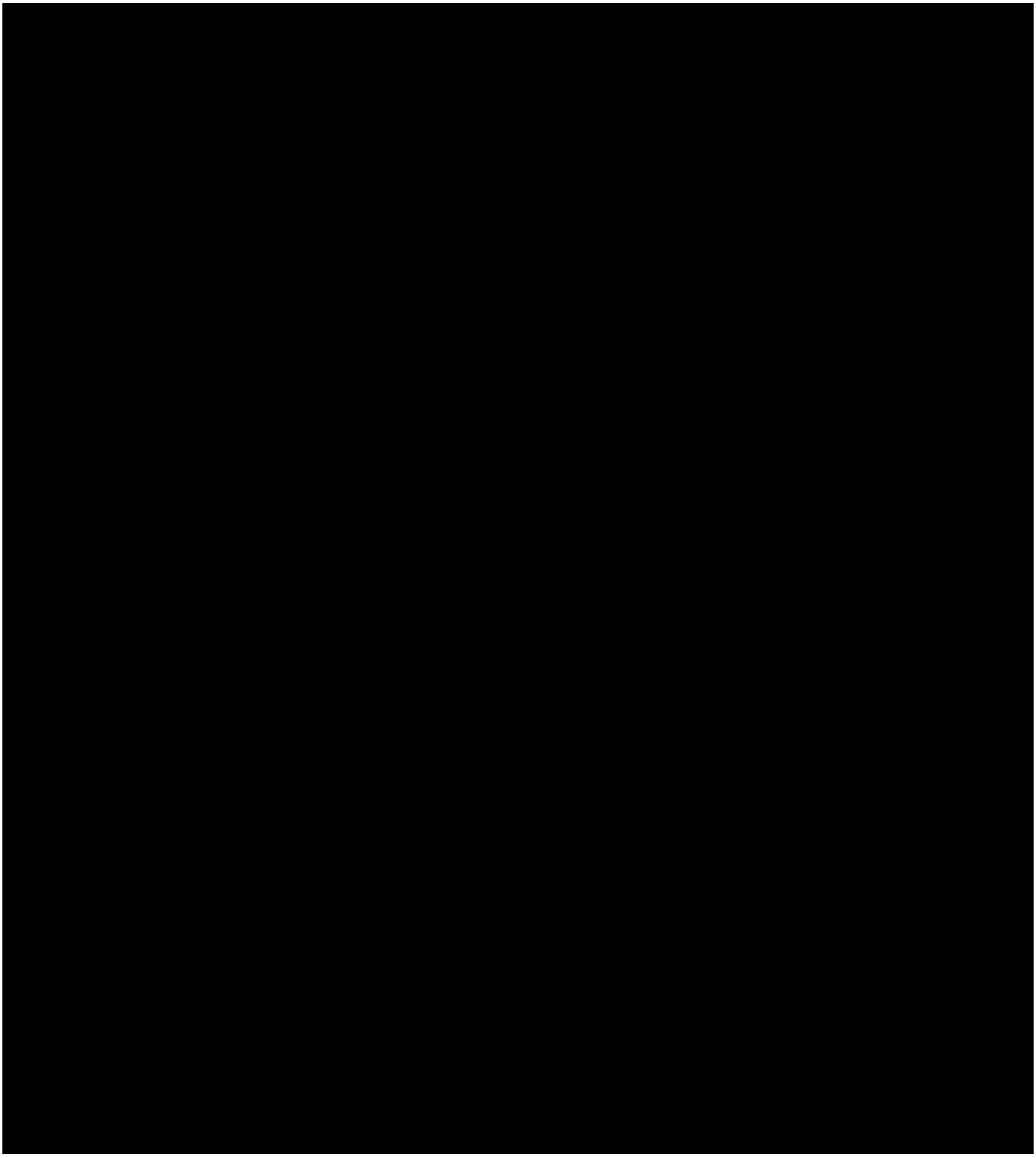
## 5. DOSING DELAYS/DOSE MODIFICATIONS

### 5.1 Dose Delays

All scheduled cycles within a course are to be given approximately four weeks apart. If necessary, a cycle may be delayed for up to one week, and subsequent cycles should continue to be four weeks apart. If delayed more than one 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.

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

- Nivolumab-related infusion reactions must resolve to baseline prior to administration of GVAX and BMS-813160.
- GVAX and BMS-813160 treatment and assessments can be resumed after the reason for delay has resolved.



[redacted]

[redacted]

## 5.2 Dose Modifications

Participants will be monitored continuously for AEs while on study therapy. Participants will be instructed to notify the study site for any and all AEs. For an AE requiring dose modification of BMS-813160, the other study treatments (i.e. GVAX and nivolumab) should be interrupted to allow recovery from the AE. If there is an AE and/or reaction (i.e. infusion reaction) to GVAX or nivolumab, all study treatments will be interrupted to allow recovery from the reaction.

All participants who discontinue study treatment should comply with protocol-specified follow-up procedures as outlined in **Section 4.11**. The only exception to this requirement is

when a participant withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (e.g. is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study treatment is discontinued prior to the participant's completion of the study, the reason for the discontinuation must be documented in the participant's medical records and entered on the appropriate Case Report Form (CRF).

### 5.2.1 Nivolumab Dose Modifications

No dose modifications (increase or decrease) to Nivolumab are allowed. Doses can be delayed for side effects. If there are delays due to AEs or reactions to GVAX and/or BMS-813160, nivolumab will also be held to allow recovery from the AE/reaction.

### 5.2.2 GVAX Dose Modifications

No dose modifications (increase or decrease) to GVAX are allowed. Doses can be delayed for side effects. If there are delays due to AEs or reactions to nivolumab and/or BMS-813160, GVAX will also be held to allow recovery from the AE/reaction.

### 5.2.3 BMS-813160 Dose Modifications

Medical management for dose delay and adverse events are outlined in **Appendix E**.

#### 5.2.3.1 Dose Reductions in BMS-813160

1) New onset of QTcF intervals > 500 msec or prolongation > 50 msec over baseline, new onset QRS intervals > 140 msec, new onset bundle branch block or symptomatic bradycardia, Type 2 second or third-degree heart block will require dose interruption and restarting at one dose level lower. Any electrolyte abnormalities should be corrected and ECG should be repeated with cardiology consultation if clinically indicated.
2) Grade 3 non-hematologic toxicity or Grade 4 non-hematologic toxicity attributed to BMS-813160 (that do not meet criteria for removal from study treatment, **Section 4.9**) will require one dose level reduction.
    - Any Grade 3 laboratory only abnormalities (that do not meet criteria for removal from study treatment, **Section 4.9**) without clinical manifestations or electrolyte abnormalities that may be managed with supplementation can be managed with dose delay and do not automatically need dose modification.
3) Participants who need a dose reduction for toxicity attributable to BMS-813160 will continue on the reduced dose of BMS-813160 for the remainder of the study.

4) BMS-813160 dose modifications are presented in **Table 3**.

#### 5.2.3.2 Guidelines for Permanent Discontinuation of BMS-813160

Participants will be required to permanently discontinue BMS-813160 for the following reasons:

1) If the participant fulfils the criteria for removal from study treatment (**Section 4.9**).
2) If a participant needs more than 2 dose reductions of BMS-813160 for toxicity, then participant will permanently discontinue further treatment with all three study drugs and be taken off treatment, unless it is determined to be in the participant's best interest to continue as per the Principal Investigator, IND Sponsor and BMS.

**Table 3: Recommended Dose Modifications for BMS-813160**

| | BMS-813160 dose | |
|---|---|---|
| Starting Dose | 300 mg BID | 150 mg BID |
| Dose Reduction 1 | 150 mg BID | 150 mg daily |
| Dose Reduction 2 | 150 mg daily | Discontinue |

## 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 5.0 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 patient, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected, recorded, and followed as appropriate.

The Principal Investigator 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 Principal Investigator, research nurse, and data manager, the Principal Investigator is ultimately responsible for grading and attribution of all events.

All adverse events experienced by patients will be collected and reported from the first dose of the investigational agent, throughout the study, and will only be followed for 4 weeks unless related to the investigational agent. Only toxicities considered related to study procedures or treatment will be collected from the time of surgery until the start of Cycle 2.

All Serious Adverse Events (SAEs) will be collected from the first day of immunotherapy treatment through 100 days after the end of treatment or until a new antineoplastic treatment is initiated, whichever occurs first. All SAEs whether related or not related to study drug must be reported to the IND Sponsor and BMS Worldwide Safety. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g. a follow-up skin biopsy).

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

**Laboratory abnormalities:** Laboratory abnormalities present at the screening visit will be recorded as pre-treatment signs and symptoms. After study treatment administration, all grade 3 and 4 clinical laboratory results that represent an increase in severity from baseline will be reported as adverse events. A grade 1 or 2 clinical laboratory abnormality should be reported as an adverse event only if it is considered clinically significant by the investigator. Any laboratory abnormality that required the participant to have a study drug discontinued or interrupted or required the participant to receive corrective therapy will be reported.

## 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 [e.g., 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
- Is a pregnancy
- Is a potential drug-induced liver injury (DILI)
- Is a suspected transmission of an infectious agent (e.g. pathogenic or nonpathogenic) via the study drug.

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

- A visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- Elective surgery, planned prior to signing consent
- 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 (e.g. 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 (e.g. lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).

Although pregnancy, overdose, potential drug-induced liver injury (DILI), and cancer are not always serious by regulatory definition, these events must be handled as SAEs (see **Section 6.5** for details).

Any component of a study endpoint that is considered related to study therapy should be reported as an SAE (e.g. death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

An SAE report should be completed for any event where doubt exists regarding its seriousness.

All SAEs will be reported to the IND Sponsor and BMS Worldwide Safety, whether related or not related to study drug.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

#### 6.1.3 Non-Serious Adverse Event

A non-serious adverse event is an AE not classified as serious.

Any significant worsening noted during interim or final physical examinations, electrocardiograms, X-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

Non-serious Adverse Events are to be provided to BMS in aggregate via interim or final study reports as specified in the agreement or, if a regulatory requirement [e.g. IND US trial] as part of an annual reporting requirement.

### 6.2 Relationship and Grading

The relationship of an AE to the administration of the study drug is to be assessed by the investigator according to the following definitions:

- No (unrelated, not related, no relation): The time course between the administration of study drug and the occurrence or worsening of the adverse event rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc.) is suspected.

- Yes (related): The time course between the administration of study drug and the occurrence or worsening of the adverse event is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified.

The following factors should also be considered:

- The temporal sequence from study drug administration - The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.

- Underlying, concomitant, intercurrent diseases - Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication - The other medications the subject is taking or the treatment the subject receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of study drug - Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses - The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- The pharmacology and pharmacokinetics of the study drug - The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

Assessment of Grade:

The investigator will make an assessment of grade for each AE and SAE reported during the study, which will be recorded in the CRF. The assessment will be based on the National Cancer Institute's CTCAE (Version 5.0) and graded as shown below:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

Any AE that changes in grade during its course will be recorded in the CRF at the highest level experience by the subject.

### 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 IND 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 nivolumab, BMS-813160 or 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.

## 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 standard of care treatment periods. The standard of care treatment periods include FOLFIRINOX-based chemotherapy administration and SBRT treatment through initiation of Cycle 1 of combination immunotherapy and from surgical resection or Nanoknife procedure through initiation of Cycle 2 combination immunotherapy. All AEs collected will be reported in aggregate in the final study report, which must be provided to BMS. No individual or expedited reporting is required.

All serious adverse events, regardless of causality to study drug, including those thought to be associated with protocol-specified procedures will be reported promptly to the IND Sponsor and BMS Worldwide Safety within 24 hours of recognition, with the exception of unrelated SAEs that occur during the standard of care treatment periods as defined above. Serious adverse events should be reported using the form found in **Appendix B**. 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.

**SAE reports and any other relevant safety information are to be sent to:**
**IND Sponsor (Elizabeth Jaffee):** [redacted]
**BMS:** [redacted]

After the initial AE or SAE report, the investigator is required to proactively follow each subject and provide further information to the safety department in regard to the subject's condition.

All AE(s) and SAE(s) will be followed until:
- Resolution

- The condition stabilizes
- The event is otherwise explained
- The subject is lost to follow-up
- Death

As soon as relevant information is available, a follow-up SAE report will be submitted to the IND Sponsor and BMS.

If it is discovered a patient is lactating, pregnant, or may have been pregnant at the time of exposure to the BMS product associated with this study (i.e. from start of study immunotherapy treatment to 5 months after study drug discontinuation), the pregnancy, AEs associated with maternal exposure, and pregnancy outcomes must be reported to the IND Sponsor and BMS within 24 hours on the approved site SAE form. If only limited information is initially available, follow up reports may be required. The original forms will remain on site. Follow-up information should be obtained on pregnancy outcomes for one year following the birth of the offspring.

Any pregnancy or lactation that occurs in a female partner of a male study participant, who has provided written consent to provide information regarding the pregnancy, that occurs during the trial to 7 months after study drug discontinuation should be reported to the IND Sponsor and BMS. Pregnancies must be reported and submitted to the IND Sponsor and BMS on a BMS Pregnancy Surveillance Form or the MedWatch, CIOMS, or approved site SAE form.

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. If the pregnancy continues to term, the outcome (health of infant) must also be reported to the IND Sponsor and BMS Worldwide Safety.

The Principal Investigator (or designee) will reconcile the clinical database SAE cases (case level only) transmitted to the IND Sponsor and BMS Global Pharmacovigilance ([redacted]. Frequency of reconciliation should be approximately every 3 months and prior to the database lock or final data summary. BMS GPV&E will email, upon request from the Investigator (or designee), the reconciliation report. Requests for reconciliation should be sent to [redacted] The data elements listed on the BMS GPV&E reconciliation report will be used for case identification purposes. If the Sponsor determines a case was not transmitted to the IND Sponsor and BMS GPV&E, the case should be sent immediately to the IND Sponsor and BMS.

Adverse events that are routinely collected according to GCP shall be submitted to BMS every three (3) months by the last working day of the third month. The adverse event information required to be sent to BMS is noted in an attached 'Bristol-Myers Squibb

Early Asset Investigator Sponsored Research (ISR) Import Plan' which describes the method of collection and submission to BMS via the mailbox: [redacted] When the file is submitted to BMS, it must be noted whether the file contains all Non Serious Adverse Events (only adverse events not previously submitted to BMS within the 3 months).

### 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 IND Sponsor.

#### 6.5.3.1 Expedited IND Safety Reports

*7 Calendar-Day Telephone or Fax Report*:
The IND 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 [redacted] to the FDA within 7 calendar days of first learning of the event.

*15 Calendar-Day Written Report*:
The IND 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 IND 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 IND 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. PHARMACEUTICAL INFORMATION

### 7.1 GVAX Pancreas Vaccine

#### 7.1.1 Agent Accountability

The IND Sponsor or the IND 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

GM-CSF-secreting, irradiated, whole cell vaccines recruit and activate tumor-specific T-cells and induce a cytotoxic response through two mechanisms: 1. they deliver a range of peptide antigens (without the need for specific knowledge of the relevant target antigens), and 2. GM-CSF is an important growth and differentiation factor for dendritic cells, which are potent antigen-presenting cells.

#### 7.1.3 Description

GVAX pancreas vaccine, PANC 10.05 pcDNA-1/GM-Neo Clinical Lot (Irradiated) and PANC 6.03 pcDNA-1/GM-Neo Clinical Lot (Irradiated) is a white, milky suspension in a 2 ml cryovial. Each of the pancreatic tumor cell lines have been genetically-modified with a plasmid vector encoding the cDNA for human GM-CSF and subsequently cultured and irradiated.

The vaccine consists of equal numbers ($2.5 \times 10^8$ each) of irradiated PANC 6.03 and PANC 10.05 cells combined into a single vaccination. Vaccine cells from each pancreas tumor cell line are frozen at $1.25 \times 10^8$ cells/vial (2 vials per cell line) in an injectable formulation of Hespan (6% hetastarch in 0.9% sodium chloride with 2% human serum albumin and 5% DMSO). The GVAX pancreas vaccine will be thawed on the day of vaccination and taken up into syringes.

### 7.1.4 **Packaging and Labeling Information**

Vial labels on each cell line will contain the cell line name, either PANC 10.05 pcDNA-1/GM-Neo Clinical Lot, (Irradiated) or PANC 6.03 pcDNA-1/GM-Neo Clinical Lot (Irradiated) along with: the lot number, cell concentration and volume, date of manufacture, vial number, storage conditions, IND caution statement and manufacturer.

### 7.1.5 **Preparation**

Detailed instructions on the preparation of GVAX pancreas vaccine for administration will be provided in the Pharmacy Manual.

### 7.1.6 **Storage**

PANC 10.05 pcDNA-1/GM-Neo Clinical Lot (Irradiated) and PANC 6.03 pcDNA-1/GM-Neo (Irradiated) must be stored in vapor phase liquid nitrogen, less than or equal to -135°C.

### 7.1.7 **Stability**

Once thawed, the GVAX pancreas vaccine must be administered to the subject within 3 hours.

### 7.1.8 **Route of Administration**

Six intradermal injections: 2 in the right thigh, 2 in the left thigh, and 2 in the non-dominant arm. If one of these limbs is contraindicated, the dominant arm may be used.

### 7.1.9 **Subject Care Implications**

There is a possible risk of anaphylaxis and should be administered in a setting where emergency treatment is available. Administration should be immediately discontinued and the appropriate therapy instituted if there is a serious allergic reaction. The subject must be observed in the clinic for at least 60 minutes after the first set of injections and 30 minutes after subsequent injections. If an anaphylactic reaction is suspected, this must be discussed with the IND Sponsor, Merck and the Principal Investigator before the subject is given another dose of vaccine.

The vaccine should not be administered to subjects with a known hypersensitivity to GM-CSF, DMSO, hetastarch, trypsin (porcine origin), or fetal bovine serum. Subjects allergic to corn can also be allergic to hetastarch. Precautions include hypersensitivity reactions and anaphylaxis. At 5-fold human doses, hetastarch is embryocidal in animals.

The vaccine should not be administered to pregnant or nursing women, to subjects with

active or untreated brain metastases, or to subjects with autoimmune disorders such as systemic lupus erythematosus, sarcoidosis, rheumatoid arthritis, glomerulonephritis, vasculitis, etc. It should not be administered to subjects who may be at increased risk for bleeding or infection from intradermal injections such as individuals who have coagulopathies or decreased bone marrow function.

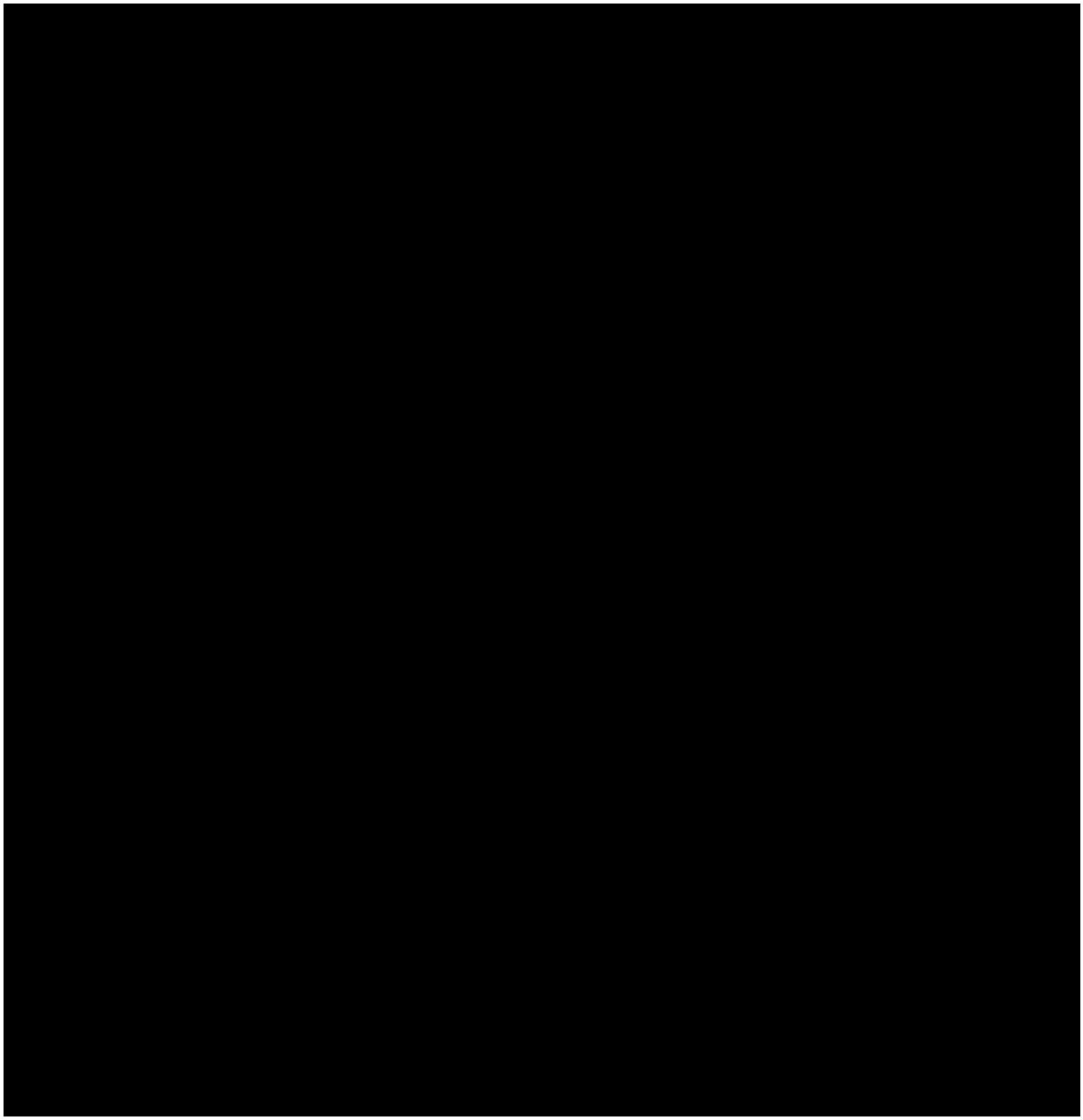
Systemic corticosteroids and immunosuppressive therapy should be avoided as they may inhibit the effectiveness of the vaccine, however, intranasal, intra-articular or topical steroids are permitted. The interaction with other vaccines is unknown.

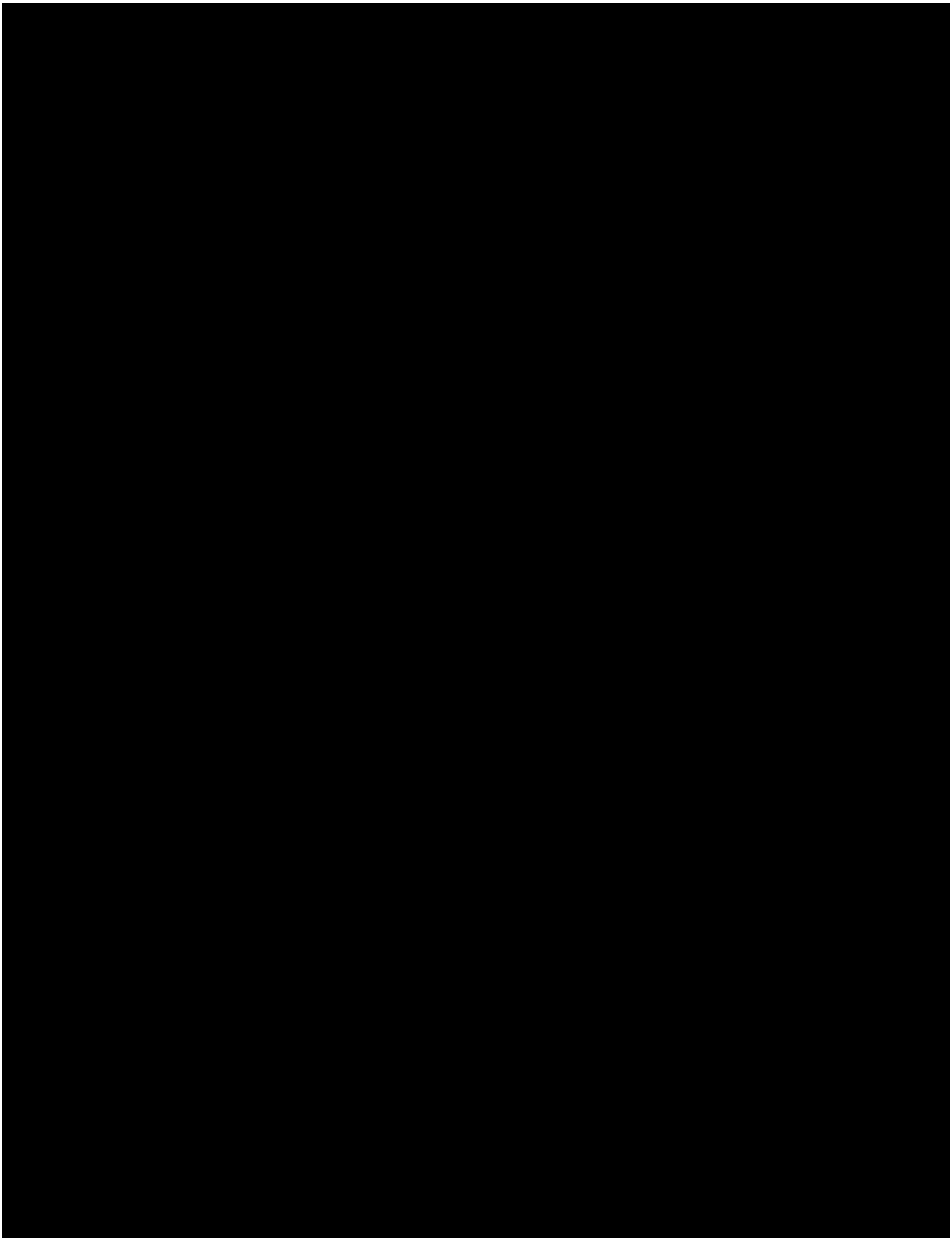
The vaccine should be used with caution in subjects with a history of cardiac arrhythmias, pericardial or pleural effusions, congestive heart failure, pulmonary infiltrates, or lung disease associated with hypoxia.

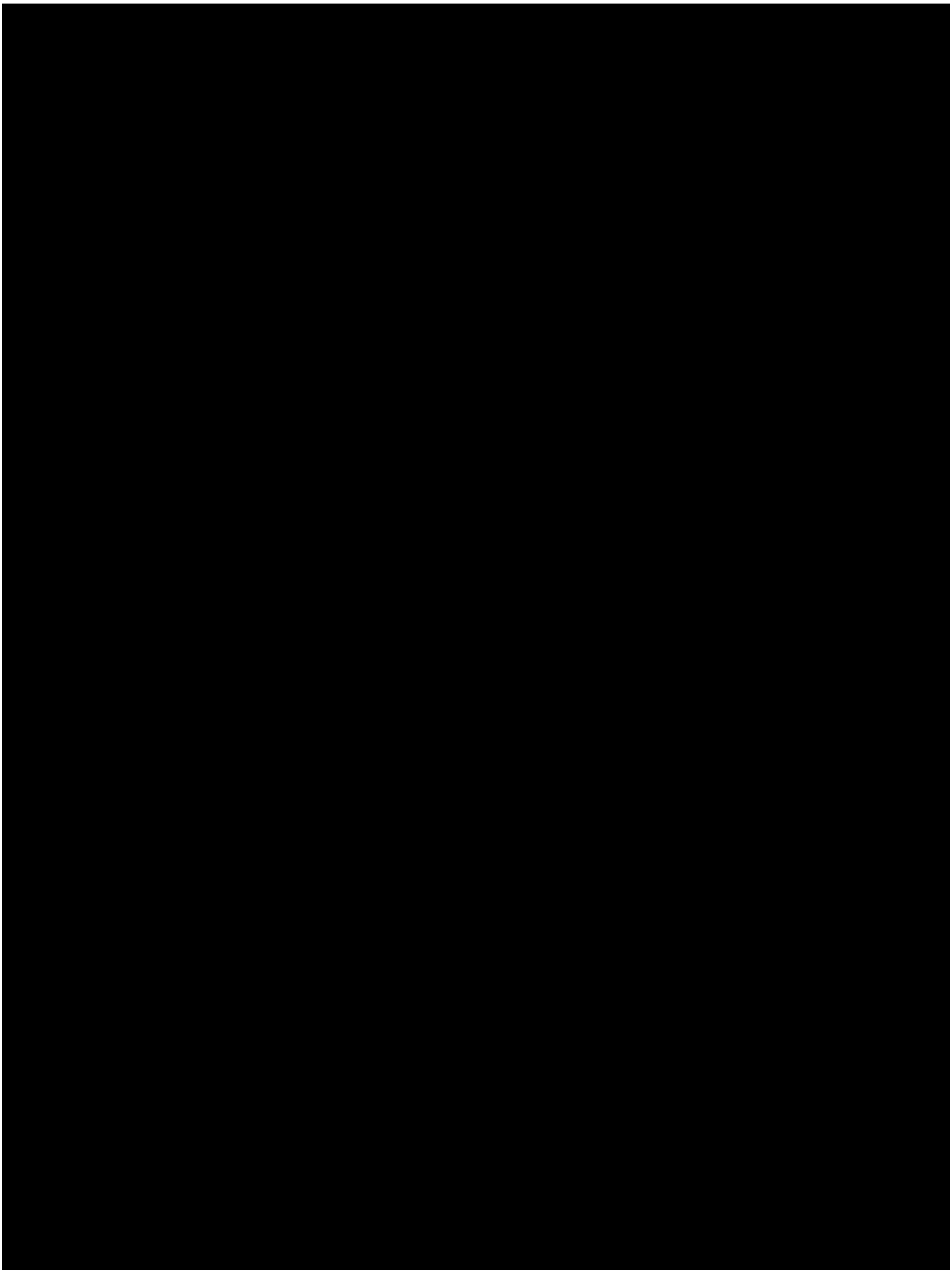
### 7.1.10 **Returns and Reconciliation**

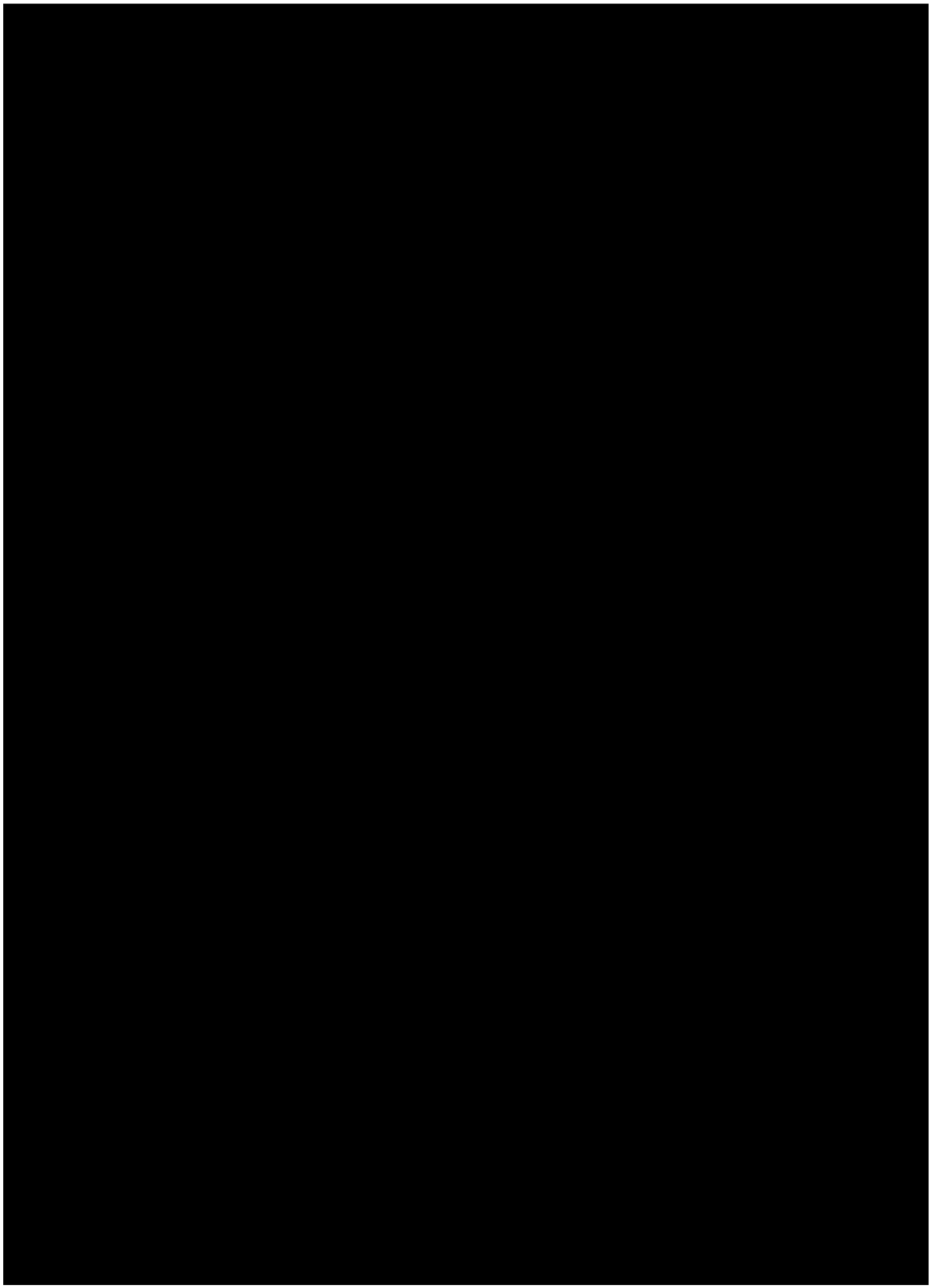
The investigator is responsible for keeping accurate records of the clinical supplies, the amount dispensed to, and returned by the subjects and the amount remaining at the conclusion of the trial.

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 are be provided in the Laboratory Manual.

### 8.1 Tumor Tissue Studies

4-6 core tumor biopsies will be collected during

1) initial study enrollment if adequate diagnostic biopsy is not available,
2) the scheduled endoscopy with fiducial placement and
3) after pre-surgical evaluation if the patient is not a surgical candidate.

The core biopsy specimens will be collected for both snap frozen specimens and FFPE slides. The core formalin samples will be placed in one FFPE tissue block.

Additional tissue will be collected during surgical resection/NanoKnife procedure if the patient is a surgical candidate. Resected PDAs will be archived for FFPE tissue slides, frozen sections and freshly isolated TILs. Detailed instructions for tissue collection, processing and shipment are provided in the procedures manual.

The patient may also have biopsies of metastases performed. 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 will 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.

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 mutated neoepitope-specific T-cell repertoire by TCR clonality and/or the MANAFEST assay and in pre- and post-treatment tumor specimens and peripheral blood lymphocyte (PBL) over time on treatment.

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

Whole blood of up to 100 mL will be collected as per the study calendar (Section 9) and used for PBL processing. During the Post-Immunotherapy Evaluation visit (Cycle 1 Day 28), additional plasma will be isolated from a portion of this sample (approximately 50 mL) while it is being processed for PBL to support the isolation of tumor infiltrating lymphocytes. Post-treatment expression of PD-1 and other lymphocyte activation markers will be measured and correlated with OS and MFS. 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).

### 8.3 Serum and Plasma Marker Studies

Sera and plasma will be collected at as per study calendar in Section 9 to identify potential therapeutic targets, biomarkers, and predictors of response and autoimmune toxicity through proteomic approaches and ctDNA isolation. Whole blood will be collected in two 10 mL Serum Separator Tube (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 -80$^{o}$C.

We will also collect whole blood in two 10 mL plasma preparation tubes 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 -80$^{o}$C. Pellets from this separation procedure will be washed in PBS and then divided into aliquots and also stored at -80$^{o}$C.

### 8.4 Diagnostic Tissue Samples

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

## 9. STUDY SCHEDULE

Patients will be evaluated and consented at the time of initial diagnosis of LAPC. Patients should meet all eligibility criteria and complete all screening procedures prior to starting SOC chemotherapy, however they can be enrolled up to one month after initiating SOC chemotherapy to allow for time to gather all records from outside institutions if necessary. Patients will then receive 8-16 14-day cycles of FOLFIRINOX-based chemotherapy, followed by SBRT between 2-4 weeks after completion of chemotherapy. Both chemotherapy and radiation therapy are standard therapies for LAPC, and will be administered off-trial. They will have another evaluation for eligibility to receive immunotherapy after completion SBRT at which point they will be randomized during Phase II and they will initiate Cycle 1 Day 1 of combination immunotherapy within 2 weeks of completion of SBRT. The patient will undergo Post-Immunotherapy Evaluation within one week after Cycle 1 Day 28.

| Pre-surgical Study Schedule | | | | | | |
|---|---|---|---|---|---|---|
| Procedure | Screening/ Baseline | Pre-Immunotherapy Screening (within 3 weeks prior to C1D1) | Cycle 1 Immunotherapy (within 2 weeks after completion of SBRT) | | | End of Cycle 1 (day before surgery or C1D28, whichever is earlier)[24] |
| | | | C1D1[2] | C1D2[3] | C1D15[4] | |
| Visit Window[1] (days) | | | - | - | +3 | -3/+14 |
| Nivolumab (All patients) | | | X | | | |
| GVAX (Phase 1 and Arm B patients) | | | | X | | |
| BMS-813160 (All patients)[5] | | | X | X | X | X |
| Eligibility criteria | X | X | | | | |
| Randomization (Phase 2 only)[6] | | X | | | | |
| Demographics | X | | | | | |
| Medical History[7] | X | X | | | | |
| Medications | X | X | X | | X | X |
| Physical Exam[8] | X | X | X | | | X |
| Vital Signs and pulse ox[9] | | X | X | X | X | X |
| Height[9] | | X | | | | |
| Weight | | X | X | | X | X |
| Performance Status | X | X | X | | X | X |
| EKG for PR, QRS and QTcF[10] | | X | X | | X | X |
| Hematology profile[11, 12] | X | X | X | | X | X |
| Chemistry profile[11, 13] | X | X | X | | X | X |
| TSH[11, 14] | | X | X | | | X |
| Serum/Urine Preg[11, 15] | X | X | X | | | |
| CA 19-9[11] | X | X | X | | | X |
| Urinalysis and microscopic exam[11, 16] | | X | | | | |
| INR[11] | | X | | | | |
| HLA-Typing[11] | | | X | | | |
| Adverse event evaluation | | X | X | | X | X |
| Vaccine Site Assessment | | | | | | X |
| PET-CT, CT, or MRI[17] | X | X | | | | X[18] |
| Tumor measurements[17] | X | X | | | | X[18] |
| Pathology Review | X | X | | | | |
| Peripheral blood for research (up to 100cc)[19] | | | X | | | X |
| Serum (20cc)[19] | | | X | | | X |
| Plasma (20cc)[19] | | | X | | | X |
| Archival Tissue[20] | X | | | | | |
| EUS Core Biopsy[19] | | X[21] | | | | X[22] |
| QoL Questionnaire[23] | | | X | | | X |

*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. 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.*

**Pre-surgical Study Schedule Footnotes**

1. Longer delays to be approved by the IND Sponsor and Principal Investigator.
2. Cycle 1 Day 1 labs do not need to be repeated if pre-immunotherapy screening labs are done within 7 days of this treatment visit.
3. Day 2 visit and assessments are not required for Arm A or Arm C patients as they do not receive GVAX
4. Day 15 visit assessments (labs, vitals, EKG) may be done locally with information regarding AEs, medications, and performance status collected via phone call or televisit
5. Anti-CCR2/5 (BMS-813160) therapy will be continued up to the day before surgery.
6. Randomization for Phase II participants will occur after re-screening eligibility criteria has been met. Due to drug availability, patients meeting re-screening eligibility after 12/19/2022 will be assigned to Arm C (not randomized).
7. 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, secondary sites of cancer, histology, histologic grade, date of initial diagnosis, prior cancer therapy regimens.
8. 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.
9. Temperature, respiration rate, blood pressure, and pulse will be taken as indicated. Pulse oximetry will be taken prior to each cycle. Nivolumab: vitals will be collected prior to and at end of the infusion (+15 min). GVAX: vitals will be collected prior to and after GVAX administration. Height from any time prior to Cycle 1 may be used.
10. QT corrected for heart rate using Fridericia's method. C1D1 EKG does not need to be repeated if Pre-Immunotherapy Screening EKG is done within 7 days of C1D1 visit.
11. Labs may be collected within a window of up to 7 days prior to dosing. Labs collected for non-dosing visits (i.e. safety labs/visits) may be collected up to 3 days prior to visit. 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.
12. CBC with differential including absolute eosinophil count, absolute neutrophils, absolute lymphocytes, and platelets.
13. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, amylase, lipase. Amylase and lipase do not need to be collected at screening prior to chemotherapy.
14. T3 and FT4 to be checked reflexively if TSH is abnormal.
15. 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).
16. Bilirubin, blood, glucose, ketones, leukocytes, nitrite, pH, color, protein, RBC and WBC count, and specific gravity.
17. 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, at pre-immunotherapy screening (within 3 weeks of C1D1), and at the time of surgical evaluation (post-immunotherapy). Non-contrast CT Chest and MRI Abdomen/pelvis will be done for those with contrast allergies.
18. This standard of care imaging is part of the pre-surgical evaluation and can be done anytime between immunotherapy and planned surgery.
19. Research samples will be collected at the discretion of the PI based on availability of supplies and safety of patient and staff. See Section 8 for information on correlative studies.
20. Archival tissue from non-study biopsies may be collected at any time throughout the study.
21. Biopsy (4-6 cores) will be done during endoscopy for fiducial placement (not tied to pre-immunotherapy screening visit timing).
22. EUS Guided biopsy will be obtained for research purposes if subject is not a surgical candidate. 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.
23. QOL survey may be completed up to 3 days prior to a visit.
24. If End of Cycle 1 window overlaps with C1 D15 window, these visits may be combined.

Surgery should be scheduled to occur between five to seven weeks after completion of SBRT. If surgery is scheduled after completion of Cycle 1 (i.e. >28 days from nivolumab dosing), anti-CCR2/5 (BMS-813160) therapy will be continued up to the day before surgery. A second dose of nivolumab and GVAX will not be administered because this is not considered a new cycle. Standard surgical procedure will be determined by the operating surgeon. The surgical procedure is considered standard of care, but must be performed at Johns Hopkins Hospital.

Post-treatment biospecimens will be obtained the following ways:

- Surgical candidate found to have resectable tumor – resected specimen will be obtained intraoperatively
- Surgical candidate found to have unresectable tumor – research core biopsies will be obtained intraoperatively
- Non-surgical candidate – EUS-guided tumor biopsy
    - Note, if a patient is noted to have developed metastases that can be safely biopsied (as determined by our interventional radiology team), they will be offered biopsy of the metastases.

For those who undergo a surgery or NanoKnife procedure, immunotherapy will be initiated within 6 to 12 weeks of the procedure. For those who are not surgical candidates, the immunotherapy will not be held.

Both resected and unresected patients will receive combination immunotherapy every 28 days for a total of 4 more cycles (cycles 2-5) or until the development of metastatic disease. Patients with local progression will be allowed to continue the study treatment. Patients will be expected to be on trial for approximately 7 to 9 months if they undergo surgery, and 6 months if they do not undergo surgery.

| Post-surgical (or Post-Surgical Evaluation) Study Schedule | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Procedure | Each Cycle of combination immunotherapy is 28 days | | | | | | | | | | | | EOT[16] | Safety FU[16] | Clinical FU[16] | Survival FU[16] |
| | C2 D1 | C2 D2[2] | C2 D15[3] | C3 D1 | C3 D2[2] | C3 D15[3] | C4D1 | C4 D2[2] | C4 D15[3] | C5 D1 | C5 D2[2] | C5 D15[3] | | | | |
| Visit Window[1] (days) | +7 | | +3 | +7 | | +3 | +7 | | +3 | +7 | | +3 | ±7 | +14 | ±14 | ±14 |
| Eligibility criteria[4] | X | | | | | | | | | | | | | | | |
| Nivolumab (All patients) | X | | | X | | | X | | | X | | | | | | |
| GVAX (Ph1, Arm B, and Arm C pts) | | X | | | X | | | X | | | X | | | | | |
| BMS-813160 (Ph1, Arm A, and Arm B pts) | X | X | X | X | X | X | X | X | X | X | X | X | | | | |
| Medications | X | | X | X | | X | X | | X | X | | X | X | X | X | |
| Physical Exam[5] | X | | | X | | | X | | | X | | | X | | X | |
| Vital Signs and pulse ox[6] | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | |
| Weight | X | | | X | | | X | | | X | | | X | | X | |
| Performance Status | X | | X | X | | X | X | | X | X | | X | X | | X | |
| EKG for PR, QRS and QTcF[7] | X | | X | X | | X | X | | X | X | | X | X | | | |
| Hematology profile [8, 9] | X | | X | X | | X | X | | X | X | | X | X | | X | |
| Chemistry profile[8,10] | X | | X | X | | X | X | | X | X | | X | X | | X | |
| TSH[8, 11] | X | | | X | | | X | | | X | | | X | | | |
| Serum/Urine Pregnancy[8, 12] | X | | | X | | | X | | | X | | | X | | | |
| CA 19-9[8] | X | | | X | | | X | | | X | | | X | | X | |
| Adverse event evaluation | X | | X | X | | X | X | | X | X | | X | X | X | X | |
| Vaccine Site Assessment | X | | | X | | | X | | | X | | | X | | | |
| CT or MRI[13] | X | | | | | | X | | | | | | X | | X | |
| Tumor measurements[13] | X | | | | | | X | | | | | | X | | X | |
| Peripheral blood for research (up to 100cc)[14] | X | | | | | | | | | | | | X | | | |
| Serum (20cc)[14] | X | | | | | | | | | | | | X | | | |
| Plasma (20cc) [14] | X | | | | | | | | | | | | X | | | |
| QoL Questionnaire[15] | X | | | | | | X | | | | | | X | | X | |
| Survival Follow-up | | | | | | | | | | | | | | | | X |

*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. 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.*

**Phase I and Phase II Arm B Schedule - Post-surgical Study Schedule Footnotes**

1. Longer delays to be approved by the IND Sponsor and Principal Investigator.
2. Day 2 visit and assessments are not required for Arm A patients as they do not receive GVAX
3. Day 15 visit assessments (labs, vitals, EKG) may be done locally with information regarding AEs, medications, and performance status collected via phone call or televisit
4. Patients who are deemed unresectable due to local progression (i.e. without metastatic disease) may continue directly to Cycle 2 immunotherapy without rescreening. No eligibility checklist is necessary for these patients.
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, and pulse should be taken at baseline, prior to nivolumab infusion, and at the end of the infusion. Pulse oximetry should be taken at baseline and prior to each nivolumab infusion.
7. QT corrected for heart rate using Fridericia's method. C2D1 EKG may be done up to 7 days prior to visit.
8. Labs and QOL survey may be collected within a window of up to 7 days prior to dosing. Labs collected for non-dosing visits (i.e. safety labs/visits) may be collected up to 3 days prior to visit. 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.
9. CBC with differential including absolute eosinophil count, absolute neutrophils, absolute lymphocytes, and platelets.
10. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, amylase, lipase.
11. T3 and FT4 to be checked reflexively if TSH is abnormal.
12. 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).
13. CT pancreas protocol: Chest, abdomen, and pelvis with contrast. Noncontrast CT Chest and MRI Abdomen/pelvis will be done for those with contrast allergies. Imaging may be performed up to 2 weeks prior to Cycle 2 Day 1 visit and up to 1 week prior to all subsequent treatment visits.
14. Research samples will be collected at the discretion of the PI based on availability of supplies and safety of patient and staff. See Section 8 for information on correlative studies.
15. QOL survey may be completed up to 3 days prior to visit. QOL survey should be attempted at EOT visit, but is not required.
16. These visits are for those patients NOT enrolling in the Maintenance Treatment Phase. The End of Treatment, Safety and Clinical Follow-up visits do not need to be completed for patients who did not receive study drug. Instead these patients will be followed every 12 weeks for information regarding future treatments, progression and survival. The End of Treatment scan does not need to be repeated if one has been performed within 6 weeks. See sections 4.10 - 4.11 for additional information. For patients continuing on Maintenance Treatment, see calendars below.

Following the 5th cycle of immunotherapy, if the patient remains free of metastatic disease, they will have the option to receive six additional 28-day cycles of maintenance immunotherapy, lasting a total of 24 weeks.

| **Maintenance Treatment Schedule** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Procedure | Each Maintenance Cycle is 28 days | | | | | | | EOT[14] | Safety FU[14] | Clinical FU[14] | Survival FU[14] |
| | C6D1 | C6D2[2] | C7D1 | C8D1 | C9D1 | C10D1 | C11D1 | | | | |
| Visit Window[1] | -1/+7 | | -1/+7 | -1/+7 | -1/+7 | -1/+7 | -1/+7 | -1/+7 | | | |
| Nivolumab (All patients) | X | | X | X | X | X | X | | | | |
| GVAX (Ph1, Arm B, and Arm C pts) | | X | | | | | | | | | |
| BMS-813160 (Ph1, Arm A, and Arm B pts) | X | X | X | X | X | X | X | | | | |
| Medications | | | | | | | | X | X | X | |
| Physical Exam[3] | X | | X | X | X | X | X | X | | X | |
| Vital Signs and pulse ox[4] | X | 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 | |
| EKG for PR, QRS and QTcF[5] | X | | X | X | X | X | X | X | | | |
| Hematology profile[6,7] | X | | X | X | X | X | X | X | | X | |
| Chemistry profile[6,8] | X | | X | X | X | X | X | X | | X | |
| TSH[6,9] | X | | X | X | X | X | X | X | | | |
| Serum or Urine Pregnancy[6,10] | X | | X | X | X | X | X | X | | | |
| CA 19-9[6] | X | | X | X | X | X | X | X | | X | |
| Adverse event evaluation | X | | X | X | X | X | X | X | X | X | |
| Vaccine Site Assessment | X | | | | | | | X | | | |
| CT or MRI[11] | X | | | | X | | | X | | X | |
| Tumor measurements[11] | X | | | | X | | | X | | X | |
| Peripheral blood for research (up to 100cc)[12] | | | | | | | | X | | | |
| Serum (20cc)[12] | | | | | | | | X | | | |
| Plasma (20cc) [12] | | | | | | | | X | | | |
| Quality of Life Questionnaire[13] | X | | | | X | | | X | | X | |
| Survival Follow-Up | | | | | | | | | | | X |

*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. 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.*

**Phase I and Phase II Arm B Schedule – Maintenance Treatment Schedule Footnotes**

1. Longer delays to be approved by the IND Sponsor and Principal Investigator.
2. Day 2 visit and assessments are not required for Arm A patients as they do not receive GVAX
3. Focused physical examinations. Exams, concomitant medication, AE assessments can be made up to 3 days prior to infusion.
4. Temperature, respiration rate, blood pressure, and pulse will be taken as indicated. Pulse oximetry will be taken at baseline and prior to each cycle. Nivolumab: vitals will be collected prior to and at end of the infusion (+15 min). GVAX: vitals will be collected prior to and after GVAX administration.
5. QT corrected for heart rate using Fridericia's method.
6. Labs and QOL survey may be collected within a window of up to 7 days prior to dosing. Labs collected for non-dosing visits (i.e. safety labs/visits) may be collected up to 3 days prior to visit. 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.
7. CBC with differential including absolute eosinophil count, absolute neutrophils, absolute lymphocytes, and platelets.
8. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, lipase, amylase.
9. T3 and FT4 to be checked reflexively if TSH is abnormal.
10. 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).
11. CT Chest, abdomen, pelvis (pancreas protocol) with contrast or non-contrast CT chest and MRI abdomen, pelvis for those with contrast allergies. Imaging can be done up to 1 week before each treatment visit.
12. Research samples will be collected at the discretion of the PI based on availability of supplies and safety of patient and staff. See Section 8 for information on correlative studies.
13. QOL survey may be completed up to 3 days prior to visit. QOL survey should be attempted at EOT visit, but is not required.
14. See section 4.10 – 4.11. The End of Treatment scan does not need to be repeated if one has been performed within 6 weeks

# 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 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 **Metastases free survival (MFS)**

MFS is defined as the duration of time from start of treatment to identification of distant metastases on imaging or death, whichever occurs first. 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.[43] The EORTC QLQ-PAN26 supplements the core questionnaire with 26 items specific for patients with pancreatic cancer.[44, 45] 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. We will offer subjects the option to complete their QoL questionnaires as an online REDCap survey within the 3 days prior to a visit or on paper the day of a visit. Patients who choose the online option will be sent a personalized link allowing their responses to be directly imported into our REDCap database. The REDCap database is HIPAA compliant and once survey responses are submitted, the link will no longer work and data will not be visible to the patients.

## 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 BMS representatives. During these meetings, the Investigator shall provide BMS 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, BMS will provide safety and applicable program updates to the IND Sponsor.

### 11.3 Monitoring

The SKCCC Compliance Monitoring Program will provide external monitoring for JHU-affiliated sites in accordance with SKCCC DSMP (Version 6.0, 02/21/2019). The SMC Subcommittee will determine the level of patient safety risk and level/frequency of monitoring. 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 Data and Safety Monitoring Board (DSMB) as detailed below.

Interim analysis of toxicity, outcome and ongoing scientific investigations will be performed at least annually by the Sidney Kimmel Comprehensive Cancer Center Data Safety Monitoring Board (SKCCC DSMB). The SKCCC DSMB will review aspects of this trial that are outlined in the responsibilities section of the Data and Safety Monitoring Board (DSMB) Guidance. If the committee decides that amendments should be made to this trial,

recommendations will be made in writing to the Study Principal Investigator. The study team will submit modifications to the IRB within 60 days of receipt from the DSMB. The Associate Director of Clinical Research, will arbitrate any disagreements between the DSMB and the study Principal Investigator. These changes may include early termination of accrual if deemed appropriate.

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

## 12. STATISTICAL CONSIDERATIONS

### 12.1 Study Design/Endpoints

This is a single center, open-label, phase I/II study to evaluate the activity of combination nivolumab and a CCR2/CCR5 dual antagonist (BMS-813160) with or without GVAX in patients with locally advanced pancreatic cancer (LAPC) in conjunction with FOLFIRINOX-based chemotherapy, radiation therapy, and possible surgical therapy.

The primary endpoints of Phase I are study-related adverse events according to National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE, Version 5.0) and incidence, nature and severity of all adverse events that occur on and after Cycle 1, Day 1 immunotherapy.

The primary endpoint of Phase II is the proportion of patients treated with nivolumab and a CCR2/CCR5 dual antagonist (BMS-813160) with or without GVAX who achieve immune response, defined as >80% increase of infiltration of CD8+CD137+ T-cell density after the treatment compared to baseline before treatment.

The secondary endpoints are study-related adverse events (for Phase II), overall survival (OS), metastasis free survival (MFS), local progression free survival (LPFS), surgical resectability rate, and pathologic response rate.

Exploratory endpoints include:

- Quality of life
- Evaluate changes in CD4+OX40+ and CD8+OX40+ cell density in pre- and post-treatment specimens via Halo-analysis.
- Evaluate changes in the expression of CCR2, CCR5, CXCR4 and PD-L1/PD-1 pathways in pre- and post-treatment specimens by nanostring analysis.
- Evaluate changes in M1 vs. M2 TAM, Teff:Treg, and MDSC by multiplex IHC.
- Evaluate, through genomic sequencing and RNA sequencing, mutated neoepitope specific T cell repertoire by TCR clonality and/or the MANAFEST assay in pre- and post-treatment tumor specimens and in peripheral blood lymphocytes over time on treatment.
- Cytokine/chemokine assays to assess changes in intratumoral inflammatory markers

- 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

### 12.2 Sample Size/Accrual Rate

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.

**Phase I:** 3-12 patients (3+3 design with Nivo+GVAX+BMS-813160 at two dose levels, primary endpoint - safety).

**Phase II:** up to 15 patients (primary endpoint - immunologic)
The first 10 patients will be randomized 1:1 into two arms:
Arm A: *nivolumab+ BMS-813160*
Arm B: *nivolumab+ BMS-813160+ GVAX*
Up to 5 additional patients will be assigned to Arm C: nivolumab + BMS-813160 in Cycle 1

Due to the availability of BMS-813160, the enrollment of Phase II Arm A and Arm B will close early before full accrual under the original protocol. An amendment is required to change the design of the phase II portion. The analysis plan is also changed accordingly. The primary endpoint remains to be immunologic response, defined in Section 12.1 above.

The analysis will be performed separately in two groups of patients receiving either nivolumab+ BMS-813160 (Group 1), or nivolumab+ BMS-813160+ GVAX (Group 2). Group 2 will include patients treated with the triplet regimen at the RP2D during both Phase II and Phase I portion. We expect up to 10 patients in Group 2 (including 6 treated at the 300mg dose in Phase I and 5 patients in Arm B of Phase II). A rate of immune response of 5% or lower is not considered worthy of further investigation, whereas immune response rate of at least 30% is consider worthy of further study.

Group 1 will have 8, up to 10, patients treated with the doublet regimen during Phase II (including up to 5 patients in Arm A and 3 to 5 patients anticipated to be enrolled to Arm C who receive nivolumab + BMS-813160 in Cycle 1 and nivolumab + GVAX from Cycle 2 and after). It allows us to make preliminary assessment of immune response.

The probability of events under different true immune response rate is as follow:

| number of responders out of 8 patients | True response rate | | | | |
|---|---|---|---|---|---|
| | 0.3 | 0.25 | 0.2 | 0.1 | 0.05 |
| >=1 | 0.943 | 0.900 | 0.832 | 0.570 | 0.337 |
| >=2 | 0.745 | 0.633 | 0.497 | 0.187 | 0.057 |
| >=3 | 0.448 | 0.321 | 0.203 | 0.038 | 0.006 |
| number of responders out of 10 patients | | | | | |
| >=1 | 0.972 | 0.944 | 0.893 | 0.651 | 0.401 |
| >=2 | 0.851 | 0.756 | 0.624 | 0.264 | 0.086 |
| >=3 | 0.617 | 0.474 | 0.322 | 0.070 | 0.012 |

### 12.3 Analysis of Primary Endpoint of Phase I - Safety Assessment

The safety analysis will be performed in all treated subjects. AE data will be listed individually and incidence of AEs summarized by system organ class and preferred terms within a system organ class for each treatment group. When calculating the incidence of AEs, each AE (based on preferred terminology defined by CTCAE version 5.0) will be counted only once for a given subject. In analyses of grade and causality, if the same AE occurs on multiple occasions, the highest grade and strongest relationship to study drug will be assumed. If 2 or more AEs are reported as a unit, the individual terms will be reported as separate experiences.

Changes in vital signs, hematology and clinical chemistry parameters from baseline to the end of the study will be examined. Toxicity will be tabulated by type and grade. Toxicities will be characterized according to the CTCAE version 5.0. Treatment-emergent changes from normal to abnormal values in key laboratory parameters will be identified.

### 12.4 Analysis of Primary Endpoint of Phase II - Immunologic Assessment

The evaluable populations for Phase II primary immunologic endpoint includes all subjects who completed one cycle of study combination immunotherapy.

CD8/OX40 and CD8/CD137 double staining will be performed by the sequential striping/staining multiplex IHC method of formalin-fixed, paraffin-embedded (FFPE) tissue slides,[35] and will be further developed into a more quantitative assay for endpoint analysis with the Perkin-Elmer-Vectra multiplex immunofluorescent staining method in the Tumor Microenvironment Core (Taube/Anders) of the Bloomberg-Kimmel Institute for Cancer Immunotherapy.

For each group, the rate of immune response will be estimated as the proportion of patients treated with nivolumab and a CCR2/CCR5 dual antagonist (BMS-813160) with or without GVAX who achieve immune response, defined as >80% increase of infiltration of CD8+CD137+ T cell density after the first immunotherapy cycle at the time of surgery or surgical evaluation if not a candidate) compared to baseline (prior to SBRT and after chemotherapy), together with the corresponding 95% confidence interval.

Furthermore, descriptive statistics for immune parameters in pretreatment tumor biopsy specimens and that in matched post-treatment tumor specimens will be computed. Percent change in the intratumoral immune parameters will be reported using descriptive statistics and displayed graphically. Comparison of primary immune parameters between pretreatment tumor biopsy specimens and matched post-treatment tumor specimens will be conducted using paired t-tests (or Wilcoxon signed rank tests if appropriate) and McNemar's tests for dichotomous or categorical variables, respectively.

### 12.5 Analysis of Secondary Endpoints – Phase II Safety Assessment

The safety analysis will be performed in all treated subjects. AE data will be listed individually and incidence of AEs summarized by system organ class and preferred terms within a system organ class for each treatment group. When calculating the incidence of AEs, each AE (based on preferred terminology defined by CTCAE version 5.0) will be counted only once for a given subject. In analyses of grade and causality, if the same AE occurs on multiple occasions, the highest grade and strongest relationship to study drug will be assumed. If 2 or more AEs are reported as a unit, the individual terms will be reported as separate experiences.

Changes in vital signs, hematology and clinical chemistry parameters from baseline to the end of the study will be examined. Toxicity will be tabulated by type and grade. Toxicities will be characterized according to the CTCAE version 5.0. Treatment-emergent changes from normal to abnormal values in key laboratory parameters will be identified.

We will monitor adverse events in phase II, and if we observe >33% unacceptable toxicities in the first 6 patients or any time afterwards in any arm, we will halt the enrollment pending safety evaluations. Specifically, we stop if:

| | | |
|---|---|---|
| Number of patients in the same arm with AE ≥ | 2 | 3 |
| In number of patients in that arm between | 2-6 | 7 - 9 |

The operating characteristics of the stopping rule for toxicity are shown below and are based on 5000 simulations:

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Risk of AE | 0.10 | 0.20 | 0.25 | 0.30 | 0.33 | 0.40 | 0.45 |
| % of Time study stops | 12.2% | 37.8% | 52.8% | 65.3% | 71.6% | 83.7% | 89.8% |
| Expected sample size | 8.66 | 7.98 | 7.57 | 7.21 | 7.03 | 6.66 | 6.45 |

### 12.6 Analysis of Secondary Endpoints – Efficacy Assessment

The secondary endpoints of interest are OS, MFS and LPFS, which are defined as the time from the study treatment initiation until death, evidence of metastatic disease or local

progression, respectively. The evaluable populations for OS, MFS and LPFS includes all subjects who receive at least one dose of study drugs (nivolumab, BMS-813160, or GVAX), and there will be a subgroup analysis for those who complete one cycle of study combination immunotherapy. If a patient is lost to follow-up, withdraws from the study or dies prior to being diagnosed with metastatic disease or local progression, or the study is ended prior to death, the patient will be considered censored at their last recorded follow-up. Kaplan-Meier survival curves will be constructed and the median survival estimates will be calculated with 95% confidence intervals using Greenwood's formula. Survival curves will be compared to historical data using log rank test. Because the study sample size is not powered for comparing the OS and MFS, comparisons with historical data will be performed for explorative purpose. Proportions of surgical resectability and pathologic response will be reported along with the corresponding binomial exact 95% confidence intervals.

Other secondary endpoints include surgical resectability and pathologic response. Surgical resectability will be determined by review of imaging and review of the subject's surgical candidacy (clinical status and tumor status) off trial after the patient completes off-trial chemotherapy and radiotherapy. 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.

### 12.7 Exploratory Analysis – Quality of Life

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 initial enrollment into study and as per study calendar (**Section 9**). 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.

### 12.8 Exploratory Analysis - Biomarkers

Pre-treatment core tumor biopsies will be taken and compared to post-treatment surgically resected or core biopsy samples. Results will be compared with those from the ongoing neoadjuvant clinical trials of GVAX+/-nivolumab for resectable PDA and of SBRT/GVAX/pembrolizumab for locally advanced PDA. Correlative studies will be done in HBIC scientific programs. Tumor infiltrating immune cells including T cells and myeloid

cells and expression of PD-L1/PD-1 and other immune checkpoints will be analyzed by the Perkin-Elmer-Vectra multiplex immunofluorescent staining in collaboration with Topalian and Taube Labs. CCR2/CCR5/CXCR4 associated pathways will be analyzed by NanoString. TCR clonality assays will be done in collaboration with the Jaffee lab. MANAFEST assays will be done in collaboration with the Pardoll lab.

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 nivolumab, GVAX, and BMS-813160 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. The evaluable population includes all subjects.

Continuous variables will be summarized with means or medians and standard deviations. Dichotomous and categorical variables will be summarized using proportions with exact 95% confidence intervals and counts, respectively. Summaries for both pre and post administration of each immunotherapy will be computed. Plots will be used to show the changes in immune response over time.

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, MFS, LPFS, surgical resectability and pathologic response. 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.

## REFERENCES


1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014;64(1): 9-29.
2. Ahlgren JD. Epidemiology and risk factors in pancreatic cancer. Semin Oncol. 1996;23(2): 241-50.
3. Loehrer PJ, Sr., Feng Y, Cardenes H, et al. Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: an Eastern Cooperative Oncology Group trial. J Clin Oncol. 2011;29(31): 4105-12.
4. Faisal F, Tsai HL, Blackford A, et al. Longer Course of Induction Chemotherapy Followed by Chemoradiation Favors Better Survival Outcomes for Patients With Locally Advanced Pancreatic Cancer. Am J Clin Oncol. 2013.
5. Chauffert B, Mornex F, Bonnetain F, et al. Phase III trial comparing intensive induction chemoradiotherapy (60 Gy, infusional 5-FU and intermittent cisplatin) followed by maintenance gemcitabine with gemcitabine alone for locally advanced unresectable pancreatic cancer. Definitive results of the 2000-01 FFCD/SFRO study. Ann Oncol. 2008;19(9): 1592-9.
6. Koong AC, Le QT, Ho A, et al. Phase I study of stereotactic radiosurgery in patients with locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys. 2004;58(4): 1017-21.
7. Herman JM, Chang DT, Goodman KA, et al. Phase 2 multi-institutional trial evaluating gemcitabine and stereotactic body radiotherapy for patients with locally advanced unresectable pancreatic adenocarcinoma. Cancer. 2015;121(7): 1128-37.
8. Jaffee EM, Schutte M, Gossett J, et al. Development and characterization of a cytokine-secreting pancreatic adenocarcinoma vaccine from primary tumors for use in clinical trials. Cancer J Sci Am. 1998;4(3): 194-203.
9. Jaffee EM, Hruban RH, Biedrzycki B, et al. Novel allogeneic granulocyte-macrophage colony-stimulating factor-secreting tumor vaccine for pancreatic cancer: a phase I trial of safety and immune activation. J Clin Oncol. 2001;19(1): 145-56.
10. Berns AJ, Clift S, Cohen LK, et al. Phase I study of non-replicating autologous tumor cell injections using cells prepared with or without GM-CSF gene transduction in patients with metastatic renal cell carcinoma. Hum Gene Ther. 1995;6(3): 347-68.
11. Lim M, Simons JW. Emerging concepts in GM-CSF gene-transduced tumor vaccines for human prostate cancer. Curr Opin Mol Ther. 1999;1(1): 64-71.
12. Soiffer R, Hodi FS, Haluska F, et al. Vaccination with irradiated, autologous melanoma cells engineered to secrete granulocyte-macrophage colony-stimulating factor by adenoviral-mediated gene transfer augments antitumor immunity in patients with metastatic melanoma. J Clin Oncol. 2003;21(17): 3343-50.
13. Dranoff G, Jaffee E, Lazenby A, et al. Vaccination with irradiated tumor cells engineered to secrete murine granulocyte-macrophage colony-stimulating factor stimulates potent, specific, and long-lasting anti-tumor immunity. Proc Natl Acad Sci U S A. 1993;90(8): 3539-43.
14. Lutz E, Yeo CJ, Lillemoe KD, et al. A lethally irradiated allogeneic granulocyte-macrophage colony stimulating factor-secreting tumor vaccine for pancreatic adenocarcinoma. A Phase II trial of safety, efficacy, and immune activation. Ann Surg.

2011;253(2): 328-35.
15. Drake CG, Jaffee E, Pardoll DM. Mechanisms of immune evasion by tumors. Adv Immunol. 2006;90: 51-81.
16. Liyanage UK, Moore TT, Joo HG, et al. Prevalence of regulatory T-cells is increased in peripheral blood and tumor microenvironment of patients with pancreas or breast adenocarcinoma. J Immunol. 2002;169(5): 2756-61.
17. Woo EY, Chu CS, Goletz TJ, et al. Regulatory CD4(+)CD25(+) T-cells in tumors from patients with early-stage non-small cell lung cancer and late-stage ovarian cancer. Cancer Res. 2001;61(12): 4766-72.
18. Curiel TJ, Coukos G, Zou L, et al. Specific recruitment of regulatory T-cells in ovarian carcinoma fosters immune privilege and predicts reduced survival. Nat Med. 2004;10(9): 942-9.
19. Ercolini AM, Ladle BH, Manning EA, et al. Recruitment of latent pools of high-avidity CD8(+) T-cells to the antitumor immune response. J Exp Med. 2005;201(10): 1591-602.
20. Laheru D, Lutz E, Burke J, et al. Allogeneic granulocyte macrophage colony-stimulating factor-secreting tumor immunotherapy alone or in sequence with cyclophosphamide for metastatic pancreatic cancer: a pilot study of safety, feasibility, and immune activation. Clin Cancer Res. 2008;14(5): 1455-63.
21. Lutz ER, Wu AA, Bigelow E, et al. Immunotherapy converts nonimmunogenic pancreatic tumors into immunogenic foci of immune regulation. Cancer Immunol Res. 2014;2(7): 616-31.
22. Soares KC, Rucki AA, Wu AA, et al. PD-1/PD-L1 blockade together with vaccine therapy facilitates effector T-cell infiltration into pancreatic tumors. J Immunother. 2015;38(1): 1-11.
23. Disis ML. Immune regulation of cancer. J Clin Oncol. 2010;28(29): 4531-8.
24. Dudley ME, Wunderlich JR, Yang JC, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol. 2005;23(10): 2346-57.
25. Hunder NN, Wallen H, Cao J, et al. Treatment of metastatic melanoma with autologous CD4+ T-cells against NY-ESO-1. N Engl J Med 2008;358(25): 2698-703.
26. Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev. 2010;236: 219-42.
27. Brown JA, Dorfman DM, Ma FR, et al. Blockade of programmed death-1 ligands on dendritic cells enhances T-cell activation and cytokine production. J Immunol. 2003;170(3): 1257-66.
28. Dong H, Strome SE, Salomao DR, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat Med 2002;8(8): 793-800.
29. Sharpe AH, Freeman GJ. The B7-CD28 superfamily. Nat Rev Immunol. 2002;2(2): 116-26.
30. Yoshimura K, Laird LS, Chia CY, et al. Live attenuated Listeria monocytogenes effectively treats hepatic colorectal cancer metastases and is strongly enhanced by depletion of regulatory T-cells. Cancer Res. 2007;67(20): 10058-66.
31. Nomi T, Sho M, Akahori T, et al. Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer.

Clin Cancer Res. 2007;13(7): 2151-7.
32. Gao Q, Wang XY, Qiu SJ, et al. Overexpression of PD-L1 significantly associates with tumor aggressiveness and postoperative recurrence in human hepatocellular carcinoma. Clin Cancer Res. 2009;15(3): 971-9.
33. Hamanishi J, Mandai M, Iwasaki M, et al. Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer. Proc Natl Acad Sci U S A. 2007;104(9): 3360-5.
34. Fourcade J, Kudela P, Sun Z, et al. PD-1 is a regulator of NY-ESO-1-specific CD8+ T-cell expansion in melanoma patients. J Immunol. 2009;182(9): 5240-9.
35. Tsujikawa T, Kumar S, Borkar RN, et al. Quantitative Multiplex Immunohistochemistry Reveals Myeloid-Inflamed Tumor-Immune Complexity Associated with Poor Prognosis. Cell Rep. 2017;19(1): 203-217.
36. Sanford DE, Belt BA, Panni RZ, et al. Inflammatory monocyte mobilization decreases patient survival in pancreatic cancer: a role for targeting the CCL2/CCR2 axis. Clin Cancer Res. 2013;19(13): 3404-3415.
37. Weitzenfeld P and Ben-Baruch A. The chemokine system, and its CCR5 and CXCR4 receptors, as potential targets for personalized therapy in cancer. Cancer Lett. 2014;352(1): 36-53.
38. Contento RL, Molon B, Boularan C, et al. CXCR4–CCR5: A couple modulating T cell functions. Proc Natl Acad Sci USA. 2008;105(29): 10101–10106.
39. Feig C, Jones JO, Kraman M, et al. Targeting CXCL12 from FAP-expressing carcinoma-associated fibroblasts synergizes with anti–PD-L1 immunotherapy in pancreatic cancer. Proc Natl Acad Sci. 2013;110(50): 20212-20217.
40. BMS-813160: Placebo-controlled, ascending multiple-dose study to evaluate the safety, pharmacokinetics and pharmacodynamics of BMS-813160 in healthy subjects (Study CV202002). Bristol Myers-Squibb Company; 2012. Document Control No. 930059372.
41. Nywening TM, Wang-Gillam A, Sanford DE, et al. Targeting tumour-associated macrophages with CCR2 inhibition in combination with FOLFIRINOX in patients with borderline resectable and locally advanced pancreatic cancer: a single-centre, open-label, dose-finding, non-randomised, phase 1b trial. Lancet Oncol. 2016;17(5): 651-662
42. BMS-813160 Clinical Study Report (Study CV202010): A doubleblind, placebo-controlled, randomized, two-stage, parallel-group adaptive design phase 2A study to evaluate the effects of BMS-813160 in subjects with type 2 diabetes mellitus and diabetic kidney disease who have residual macroalbuminuria despite treatment with an inhibitor of the rennin-angiotensin system. Bristol Myers-Squibb Research and Development; 2015. Document Control No. 930095738.
43. Groenvold M, Klee MC, Sprangers MA, Aaronson NK. Validation of the EORTC QLQ-C30 quality of life questionnaire through combined qualitative and quantitative assessment of patient-observer agreement. J Clin Epidemiol. 1997;50(4): 441-50.
44. Fitzsimmons D, Kahl S, Butturini G, et al. Symptoms and quality of life in chronic pancreatitis assessed by structured interview and the EORTC QLQ-C30 and QLQ-PAN26. Am J Gastroenterol. 2005;100(4): 918-26.
45. Fitzsimmons D, Johnson CD. Quality of life after treatment of pancreatic cancer. Langenbecks Arch Surg. 1998;383(2): 145-51.

## 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: SAE Reporting Form**

# Serious Adverse Event Reporting Form

**Please notify the following within 24 hours:**
**IND Sponsor ([redacted])**
**BMS [redacted])**

| | | | |
|---|---|---|---|
| **Protocol Title:** | **Phase I/II of nivolumab and BMS-813160 with or without GVAX in patients with locally advanced pancreatic ductal adenocarcinomas** | | |
| **Protocol #: J18XXX, BMS CV202-105** | **Principal Investigator:** | **Signature of PI:** | **Date:** |

| | | | |
|---|---|---|---|
| **Report Type:**<br>☐ **Initial**<br>☐ **Follow-up**<br>☐ **Final Follow-up**<br>☐ **Death**<br>☐ **Addendum to:** | **Serious Criteria / Outcome (check all that apply):**<br>☐ Death<br>☐ Life-threatening<br>☐ Hospitalization or Elongation of Existing Hospitalization<br>☐ Persistent or Significant Disability<br>☐ Congenital Anomaly<br>☐ Other Important Medical Event<br>☐ Cancer<br>☐ Overdose | **Date Event Discovered:**<br><br>**Hospital Admission Date:** | **SAE ID:**<br><br>**Hospital Discharge Date:** |

**Section A: Subject Information**

| | | | |
|---|---|---|---|
| **Subject ID:** | **Subject Age:** | **Subject Ethnicity/Race:** | **Subject Gender:**<br>☐ **Male**<br>☐ **Female** |

**Section B: Event Information**

| | |
|---|---|
| **Event diagnosis or symptoms:** | **Event Grade (CTCAE v5.0):** |
| | **Event Onset Date:** |
| | **Event End Date:** |
| | **Date of Death (if applicable):** |

| **Event Relationship to:** | **BMS-813160** | **Nivolumab** | **GVAX** | **Underlying Disease** |
|---|---|---|---|---|
| **Unrelated** | ☐ | ☐ | ☐ | ☐ |
| **Related** | ☐ | ☐ | ☐ | ☐ |

**Section C: Study Drug Information**

**Investigational Product** (cycles are 28 days):

Part 1 / Part 2 Arm B: BMS-813160 150 or 300 mg PO BID Days 1-28, Nivolumab 480 mg IV Day 1, GVAX 5x108 cells SubQ Day 2

Part 2 Arm A: BMS-813160 PO BID Day 1-28, Nivolumab 480 mg IV Day 1

**Indication:** pancreatic adenocarcinoma

| | **BMS-813160** | **Nivolumab** | **GVAX** |
|---|---|---|---|
| **Dose and Route:** | | 480 mg IV | $5x10^8$ cells SubQ |
| **Date of First Dose:** | | | |
| **Date of Last Dose Prior to Event:** | | | |
| **# of Total Doses:** | | | |
| **Action Taken w/ study drug** | ☐None ☐Interrupted ☐Discontinued ☐Delayed | ☐None ☐Interrupted ☐Discontinued ☐Delayed | ☐None ☐Interrupted ☐Discontinued ☐Delayed |
| **Event Abated after use stopped/ reduced?** | ☐Yes ☐No ☐N/A | ☐Yes ☐No ☐N/A | ☐Yes ☐No ☐N/A |
| **Event Reappeared After Reintroduction?** | ☐Yes ☐No ☐N/A | ☐Yes ☐No ☐N/A | ☐Yes ☐No ☐N/A |

**Section D: Brief Description of the Event**

**Section E: Relevant Medical History**

| Section F: Relevant Tests/Laboratory data (including dates): | | | | | |
|---|---|---|---|---|---|
| | | | | | |
| **Section G: Concomitant Drug (Not related to SAE)** | | | | | |
| **Name of the Drug** | **Start Date** | **Stop Date** | **Route** | **Dose** | **Frequency** |
| | | | | | |
| | | | | | |
| **Section H: Comments** | | | | | |
| **Additional Documents:** ☐ Please specify | | | | | |
| | | | | | |

This SAE form facilitates reporting of one SAE only. In case of multiple SAEs, a separate form should be used to report each additional SAE. Overdose must be reported as a separate SAE.

## APPENDIX C: CYP3A4 and P-GP Guidance

The lists below are not meant to be all-inclusive. Please consult individual drug labels for further information. Additional information is also available at:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

### Table I: Classification of In Vivo Inhibitors of CYP Enzymes

| CYP Enzymes | Strong Inhibitors[a] (≥ 5-fold Increase in AUC or > 80% Decrease in CL) | Moderate Inhibitors[b] (≥ 2 but < 5-fold Increase in AUC or 50-80% Decrease in CL) | Weak Inhibitors[c] (≥ 1.25 but < 2-fold Increase in AUC or 20-50% Decrease in CL) |
|---|---|---|---|
| CYP3A | boceprevir, clarithromycin, conivaptan, grapefruit juice,[d] indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil,[e] nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole | amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice,[d] imatinib, verapamil | Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo,[f] goldenseal,[f] isoniazid, nilotinib, oral contraceptives, ranitidine, ranolazine, tipranavir/ritonavir, zileuton |

Please note that this is not an exhaustive list.

Abbreviations: AUC = area under the concentration-time curve; CYP = cytochrome P450.

a. A strong inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a substrate for that CYP by equal or more than 5-fold.

b. A moderate inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 5-fold but equal to or more than 2-fold.

c. A weak inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 2-fold but equal to or more than 5-fold.

d. The effect of grapefruit juice varies widely among brands and is concentration, dose, and preparation dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (eg, high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (eg, low dose, single strength).

e. Withdrawn from the United States market because of safety reasons.

f. Herbal product.

**Table II: Classification of In Vivo Inducers of CYP Enzymes**

| **CYP Enzymes** | **Strong Inhibitors** (> 80% Decrease in CL) | **Moderate Inhibitors** (50-80% Decrease in CL) | **Weak Inhibitors** (20-50% Decrease in CL) |
|---|---|---|---|
| CYP3A | Avasimibe,[a] carbamazepine, phenytoin, rifampin, St. John's wort[b] | Bosentan, efavirenz, etravirine, modafinil, nafcillin | Amprenavir, aprepitant, armodafinil, echinacea,[c] pioglitazone, prednisone, rufinamide |

Please note that this is not an exhaustive list.
Abbreviations: AUC = area under the concentration-time curve; CYP = cytochrome P450.
a. Not a marketed drug.
b. The effect of St. John's wort varies widely and is preparation dependent.
c. Herbal product.

**Table III: Examples of clinical inhibitors for transporters**

| **Transporter** | **Inhibitors** (≥2 fold increase in digoxin AUC with co-administration) |
|---|---|
| P-gp | Amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, verapamil |

Please note that this is not an exhaustive list.
Abbreviations: AUC = area under the concentration-time curve

# 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

Subject Initials: _____

Date: _____

ENGLISH

| 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 |

Subject Initials: _____

Date: _____

## 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

Subject Initials: _____

Date: _____

ENGLISH

| 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 |