TITLE: A Phase II Clinical Trial of GVAX Pancreas Vaccine (with Cyclophosphamide) in Combination with Nivolumab and Stereotactic Body Radiation Therapy (SBRT) Followed by Definitive Resection for Patients with Borderline Resectable Pancreatic Adenocarcinoma

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1. SCHEMA

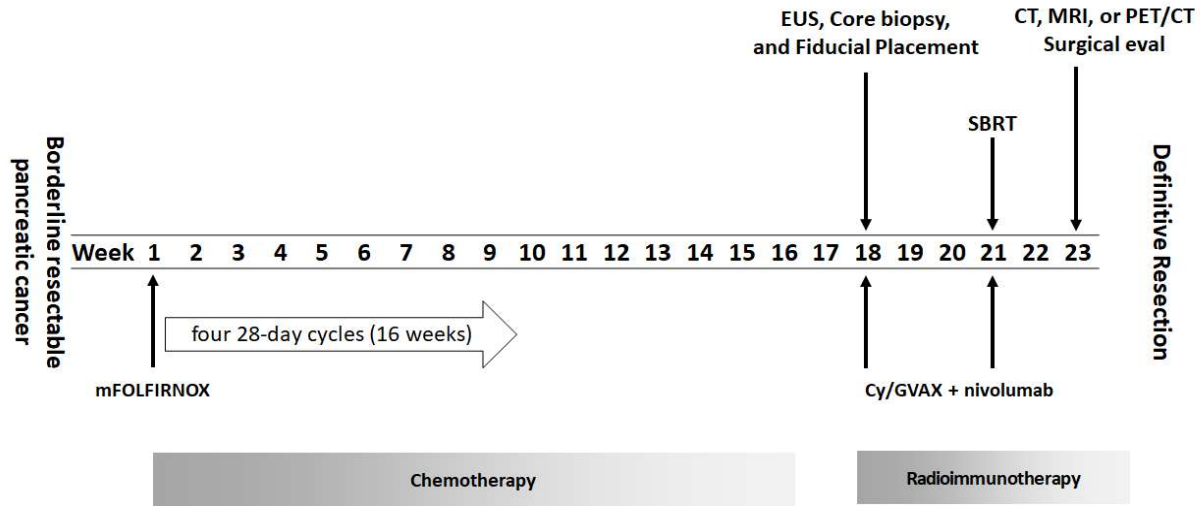

Figure 1*: Overview of the treatment plan for subjects who are enrolled in this clinical trial.*

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2. OBJECTIVES

2.1 Primary Objectives

2.1.1 To determine whether the CD8 count in the tumor microenvironment is higher for patients with borderline resectable pancreatic ductal adenocarcinoma (BR-PDAC) treated with neoadjuvant sequential chemotherapy, SBRT, and Cy/GVAX/nivolumab immunotherapy as compared to that observed in archived samples from patients treated with FOLFIRINOX and SBRT.

2.2 Secondary Objectives

2.2.1 To determine the pathologic complete response (pCR) rate at surgical resection of BR-PDAC treated with neoadjuvant sequential chemotherapy, SBRT, and Cy/GVAX/nivolumab immunotherapy.

2.2.2 To assess the safety and tolerability of sequential neoadjuvant chemotherapy, SBRT, and Cy/GVAX/nivolumab immunotherapy.

2.3 Exploratory Objectives

2.3.1 To determine the percentage of patients with BR-PDAC who obtain an R0 resection at week 25 following neoadjuvant chemotherapy, SBRT, and Cy/GVAX/nivolumab immunotherapy.

2.3.2 To determine the objective response rate (ORR) at week 25, in patients with BR-PDAC treated with sequential neoadjuvant chemotherapy, SBRT, and Cy/GVAX/nivolumab immunotherapy.

2.3.3 To determine the overall survival (OS), 12 month OS, 18 month OS, and 24 month OS, of subjects with BR-PDAC treated with sequential neoadjuvant chemotherapy, SBRT, and Cy/GVAX/nivolumab immunotherapy.

2.3.4 To evaluate the distant metastasis free survival (DMFS), 12 month DMFS, 18 month DMFS, and 24 month DMFS, of subjects with BR-PDAC receiving sequential neoadjuvant chemotherapy, SBRT, and Cy/GVAX/nivolumab immunotherapy.

2.3.5 To explore changes to the tumor microenvironment (TME) induced by sequential neoadjuvant chemotherapy, SBRT, and Cy/GVAX/nivolumab immunotherapy, and explore correlations between immune markers and clinical outcomes.

2.3.6 To assess tumor burden, mutational status, and immune dynamics through circulating biomarkers in serial collections of sera and plasma at baseline and throughout treatment.

2.4 Primary Endpoints

2.4.1 The CD8 count in resected tumor samples from patients in the study compared with historical controls.

2.5 Secondary Endpoints

2.5.1 pCR rate at week 25, as defined by no residual cancer in the primary pancreatic tissue or nodes (ypT0ypN0).

2.5.2 Adverse events as graded by NCI CTCAE version 4.03

2.6 Exploratory Endpoints

2.6.1 Percentage of subjects who receive an R0 surgical resection following neoadjuvant treatment with chemotherapy, SBRT, and Cy/GVAX/nivolumab immunotherapy.

2.6.2 ORR at week 25, defined as the proportion of patients achieving a complete response (CR) or partial response (PR) based on the Response Evaluation Criteria in Solid Tumors (RECIST 1.1)

2.6.3 The overall survival (OS)

2.6.4 Distant metastasis free survival (DMFS), defined as the time from enrollment to distant metastasis, or death.

2.6.5 Intratumoral immune infiltrates pre- and post-treatment biopsy specimens will be studied using immunohistochemistry (IHC) and transcriptional analysis.

2.6.6 Serum level of CA 19-9, and exploratory circulating biomarkers including plasma tumor DNA (ptDNA).

3. STUDY DESIGN

This is a multi-center, single arm, open label, phase II clinical trial to evaluate the safety and clinical activity of a combination of neoadjuvant Cy/GVAX/nivolumab immunotherapy following standard chemotherapy in patients with borderline resectable pancreatic ductal adenocarcinoma (BR-PDAC).

We will enroll up to 32 subjects with BR-PDAC diagnosed based upon criteria defined by the 2009 consensus statement issued by The Americas Hepatopancreatobiliary Association (AHPBA)/Society for Surgery of the Alimentary Tract (SSAT)/Society of Surgical Oncology (SSO)/National Comprehensive Cancer Network (NCCN), assessed by review of imaging and pathology at our institutional multidisciplinary pancreatic tumor clinic and tumor board [1].

Patients with BR-PDAC according to CT, PET, or MRI imaging will receive between two to eight

(recommended four) 28-day cycles of FOLFIRINOX based chemotherapy or other standard chemotherapy. After receiving the last dose of chemotherapy, patients at select sites will subsequently undergo EUS-guided fiducial placement along with an SBRT simulation, core biopsy of the pancreas tumor and research blood draws. Within two to six weeks after receiving the last dose of standard chemotherapy, participants will receive their first dose of combination immunotherapy, consisting of cyclophosphamide (Cy) 200 mg/m^2 given intravenously (IV) and nivolumab 240mg (flat dose) IV on day 1 followed by 5 x 10^8 GVAX vaccine cells, administered as six intradermal injections, on day 2. Approximately three weeks later, subjects will receive their second dose of combined immunotherapy on the same day as initiation of SBRT (6.6 Gy x 5 days, or a similar six day treatment at the discretion of the treating radiation oncologist).

After completion of immunotherapy and SBRT, patients will undergo repeat imaging with FDG-PET, CT, or MRI to evaluate for metastatic disease, progression, and/or surgical resectability. If participants are deemed a surgical candidate, they will be offered definitive surgical resection. After receiving definitive surgical resection, or if definitive resection is not performed, patients will be off study treatment and can continue with standard of care evaluations and treatment. However, patients will continue to be followed through periodic phone calls or mail to determine their clinical outcome after surgery. Patients will remain on study until death, withdrawal of consent, or completion or withdrawal of the study. Subjects who have received at least one dose of study treatment will be offered enrollment in a long-term follow-up study and continue to be evaluated for survival once they have been followed for 2 years per protocol or the study closes (**Section 7.10**).

The primary endpoint is the CD8 count in resected tumor samples from patients in the study compares with historical control samples. Secondary endpoints and exploratory objectives (described above) will also be evaluated.

4. BACKGROUND

4.1 Study Disease(s)

Pancreatic ductal adenocarcinoma (PDAC) remains the fourth leading cause of cancer mortality in adults. Although 20-30% of patients are eligible for a pancreaticoduodenectomy, the reported median survival is only 13-20 months [2]. The addition of adjuvant radiation and/or chemotherapy has demonstrated limited improvement in survival [3]. New multidisciplinary therapeutic approaches are needed for all stages of this disease.

The entity of borderline resectable PDAC (BR-PDAC) is generally defined by disease that is neither definitely resectable nor definitely unresectable. Although different anatomical definitions of BR-PDAC have been proposed, no single definition is universally accepted. In 2009, a definition of BR-PDAC was put forth by The Americas Hepatopancreatobiliary Association (AHPBA)/Society for Surgery of the Alimentary Tract (SSAT)/Society of Surgical Oncology (SSO), that has also been adopted by the National Comprehensive Cancer Network NCCN. This consensus definition will be used in this clinical trial. In this definition, pancreatic cancer is borderline resectable if there is (1) venous involvement of the superior mesenteric vein/portal vein (SMV/PV) demonstrating tumor abutment,

encasement, or short segment venous occlusion, but with suitable vessel proximal and distal to the area of vessel involvement, allowing for safe resection and reconstruction; (2) gastroduodenal artery encasement up to the hepatic artery and short segment encasement/direct tumor abutment of the hepatic artery with no extension to the celiac axis; or (3) tumor superior mesenteric artery (SMA) involvement < 180° [4].

The optimal management of BR-PDAC remains somewhat undefined. Although large randomized trials have established therapeutic standards for patients with resectable and metastatic PDAC [5,6], borderline resectable disease is still managed in a heterogeneous manner. A strong rationale exists for the use of preoperative therapy followed by surgery in patients with BR-PDAC, because upfront surgery in these patients results in a high probability of incomplete resection. This is especially important because the prognosis of resected pancreatic cancer is highly dependent on margin status. Patients with total excision and negative margins (R0 resection) have a better prognosis than those with positive margins (R1 resection) and patients with residual gross tumor (R2 resection) have a prognosis that is similar to non-operative therapy, inferring no benefit from surgery at all [7]. Although neoadjuvant chemotherapy implies a greater chance of complete resection than upfront surgery, the majority of data relating to this disease stage have been generated from a handful of single institution case series in which patients received a variety of treatment regimens [8,9]. The only historical multi-institutional trial ever designed to specifically study this population, Eastern Cooperative Group (ECOG) Trial 1200 [10], closed prematurely almost a decade ago for multiple reasons including the absence of a well-defined study population and the absence of therapeutic and surgical standards. Indeed, the ongoing failure to study borderline resectable PDAC can be attributed in large part to the historical absence of a standardized infrastructure of definitions, decision-making processes and technical procedures that is required to properly evaluate and treat this complex population [11].

More recently, the Alliance for Clinical Trials in Oncology (Alliance), Southwest Oncology Group (SWOG), Eastern Cooperative Oncology Group (ECOG), and Radiation Therapy Oncology Group (RTOG), collaborated to conduct a multi-institutional treatment trial for patients with borderline resectable PDAC (Alliance A021101). Patients on this protocol received neoadjuvant modified FOLFIRINOX (infusional 5-FU, oxaliplatin, leucovorin and irinotecan) followed by chemoradiation (CRT). Although final results of this trial have not been published at this time, initial results were reported at the ASCO annual meeting in mid-2015 [12]. Encouragingly, radiologic responses (by RECIST criteria) were observed in 6 of 23 (26%) enrolled patients, and the efficacy of this preoperative regimen was further supported by a 93% rate of R0 resection and 9% pathologic CR rate. These results provided initial support for neoadjuvant therapy in BR-PDAC.

Each year, less than 5,000 patients with resectable PDAC undergo potentially curative resection in the United States. An additional 16,000 patients are diagnosed with locally advanced PDAC. Of these, approximately 30% (5000 patients annually) might be considered to have borderline resectable primary cancers using modern definitions [4,13]. In many cases such patients are treated with palliative chemotherapy as though they are inoperable/incurable. If these patients were treated with aggressive neoadjuvant systemic therapy and SBRT, with successful pathologic down-staging of their tumor, followed by

definitive resection, there is the potential to significantly increase the percentage of PDAC achieving potentially curative therapy.

4.2 GVAX pancreas vaccine

4.2.1 *Rationale for the GM-CSF-modified allogeneic tumor cell vaccine in pancreatic cancer immunotherapy.*

The use of whole-cell vaccines is promising because it delivers a range of peptide antigens without the need for specific knowledge of the relevant target antigens [14–21]. Preclinical studies show that GM-CSF is the cytokine most effective in inducing anti-tumor immunity [16–21]. GM-CSF is an important growth and differentiation factor for dendritic cells, which are potent antigen-presenting cells (APCs) that can take up cellular proteins that encode for tumor antigens. The use of allogeneic tumor cells for vaccine development over autologous tumor cells is attractive for several reasons. Autologous tumor cells are unavailable or technically infeasible to produce. In addition, the characterization of tumor-associated antigens in melanoma revealed that most tumors share common antigens regardless of HLA type [14–21]. Furthermore, both preclinical and human data demonstrate that GM-CSF vaccine-induced host derived APCs rather than the tumor cells themselves prime $CD8^+$ T cells [14–21]. Importantly, we previously reported that the allogeneic GM-CSF pancreatic vaccine induced CD8+ mesothelin specific T cells in patients who demonstrated prolonged disease-free and overall survival in phase I and II testing [22,23]. Thus, the vaccine cells and the host do not have to be HLA compatible to prime effective CD8+ T cell responses against pancreatic tumor antigens.

4.2.2 *Results of a Phase I study of an allogeneic GM-CSF-secreting tumor vaccine in patients with resected pancreatic cancer treated at Johns Hopkins Medicine (JHMI).*

This study was the first clinical trial to test the hypothesis that allogeneic GM-CSF secreting pancreatic tumor cell lines can prime a systemic immune response in patients with resected pancreatic adenocarcinoma [18]. Fourteen patients with stage 2 or 3 disease received an initial vaccination 8 weeks following resection. This was a dose escalation study in which patients each received 10^7, $5X10^7$, 10^8, and $5X10^8$ vaccine cells. Study patients were jointly enrolled in an adjuvant chemoradiation protocol for 6 months, then given 3 additional vaccinations one month apart at the same original dose that they received for the first vaccination. Toxicities were limited to grade I/II local reactions at the vaccine site, and self-limited systemic rashes. Systemic GM-CSF levels were evaluated as an indirect measure of the longevity of vaccine cells at the immunizing site. GM-CSF levels peaked at 48 hours following vaccination. The vaccine sites were also evaluated as a measure of the local immune reaction to the vaccine. Eleven of 14 patients demonstrated a local inflammatory response, similar to what has been observed in pre-cinical models and autologous GM-CSF vaccine clinical trials. Post-vaccination delayed-type hypersensitivity (DTH) responses to autologous tumor cells were observed in 1 of 3 (33%) patients receiving 10^8 and in 2 of 5 (40%) patients receiving $5X10^8$ vaccine cells.

4.2.3 *Results of a follow-up phase II study of the GM-CSF-secreting pancreatic tumor vaccine.*

We completed a follow-up adjuvant study (study J9988) in 60 patients (88% lymph node positive) with operable pancreatic cancer[23]. Patients received an initial vaccination ($5x10^8$) 8 weeks after pancreaticoduodenectomy, followed by chemoradiation, and then 4 more immunizations with the vaccine. Primary endpoints of this trial were to: 1) estimate the disease-free and overall survival benefit associated with this treatment; 2) further characterize the toxicities associated with the vaccine; 3) assess the induction of mesothelin-specific T cell responses and correlate with clinical response rates. With a follow-up of median follow up of 25.1 months, median disease-free survival is 17.3 months (95% CI: 13.4 – 19.1) with median survival of 24.8 months (95% CI: 21.2 - 31.6). A non-matched cohort analysis comparing patients to the Johns Hopkins Surgery database treated concurrently with similar adjuvant chemoradiation suggest that there might be an initial improvement for immunotherapy treated patients during the first 2 years of treatment.

Based on the analysis, the study concluded that the administration of the GM-CSF allogeneic cancer vaccine is safe and well tolerated. Treatment related side effects were similar to those side effects seen in the phase I study. The most common side effects were vaccine injection site reactions of induration and erythema that were transient in all research participants. In addition, some subjects also had transient vaccine injection site reactions of tenderness and pruritus. The systemic reactions included transient elevation in eosinophil counts, rashes and flu-like symptoms that have included low grade fever, chills, malaise, arthralgias, myalgias, and fatigue. Most patients had a transient elevation in their eosinophil count which demonstrates the bioactivity of GM-CSF. All vaccine related toxicities have been of the same intensity and duration as those observed in the phase I study [18].

4.2.4 *Phase II Study of the GM-CSF allogeneic vaccine alone and given in sequence with immune modulating doses of IV Cyclophosphamide in subjects with advanced (Stage 4) pancreatic cancer*

A feasibility study of the GM-CSF allogeneic vaccine administered alone or in sequence with Cyclophosphamide in subjects with advanced pancreatic cancer has been completed[24]. This study was an open label multi-center study sponsored by Cell Genesys, Inc in collaboration with US Oncology. Subjects were enrolled into one of two cohorts: Cohort A- 30 subjects administered a maximum of six doses of the same pancreatic cancer vaccine as described above using the two pancreas cancer cell lines each delivering 2.5×10^8 cells intradermally administered at 21 day intervals; Cohort B- 20 subjects administered cyclophosphamide 250 mg/m2 IV one day prior to vaccine as in Cohort A. The primary objective was to evaluate the safety and induction of immune responses when treated with either vaccine alone or in sequence with cyclophosphamide. Secondary objectives include time to disease progression (TTP), median overall survival (OS), and assessment of the feasibility of detecting mesothelin-specific T cell responses in patients with advanced pancreatic cancer.

From this study, we concluded that the administration of a GM-CSF allogeneic pancreatic cancer vaccine is safe, feasible, and tolerated both alone and when given in sequence with cyclophosphamide. It was well-tolerated by patients with advanced pancreatic cancer, and the majority of these patients had received two or more prior chemotherapy regimens. The

median number of vaccines administered was 2 in Cohort A and 3 in Cohort B. Treatment related adverse events reported in > 5% of subjects included local vaccine injection site reactions (100%), fever (14%), rigors (10%) and rash (6%).

Stable disease was noted in 16.7% of subjects in Cohort A (vaccination alone) and 40% of subjects in Cohort B (vaccination plus Cytoxan). Median survival in Cohort A and Cohort B were 2.3 months and 4.7 months respectively in a subject population that had received ≥ 2 prior chemotherapies in 12/20 (60%) subjects for Cohort B and in 30/50 (60%) subjects overall. This compares well with what is reported for first and second line therapy in this patient population. Furthermore, mesothelin-specific T cell responses have been observed in treated patients. Interestingly, unlike patients with resected cancer, mesothelin-specific T cell responses can be detected at baseline, prior to vaccination, in patients with metastatic pancreatic cancer. In addition, there was some evidence of prolonged progression-free survival in those patients who demonstrated persistent mesothelin-specific T cell responses with therapy but it did not achieve statistical significance. These data would suggest that even in metastatic patients, tumor-specific T cells can be detected.

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

4.2.5 *Clinical study of ipilimumab vs. GVAX + ipilimumab for treatment of advanced unresectable PDA*

The Phase 1b study of ipilimumab (IPI, anti-CTLA-4 blockade antibody) versus GVAX + IPI in advanced PDA represents the first clinical study of a checkpoint inhibitor in combination with a vaccine for PDA[25]. Thirty patients with previously treated PDAC were randomized 1:1 to IPI at 10mg/kg alone (arm 1) or in combination with GVAX (arm 2). Patients received 4 induction doses of IPI or GVAX/IPI at 3-week intervals and then maintenance with the same treatment every 3 months. CA19-9 declines in association with GVAX + IPI treatment were seen for 7/15 (47%) patients. In contrast, 0/15 (0%) patients receiving IPI alone had CA19-9 declines. Median overall survival (OS) was 3.7 months for arm 1 and 5.7 months for arm 2 (p=0.072). The percentage of patients alive after one year also favored the combination arm (7% vs 27%). The best RECIST response was stable disease (SD) in two patients in arm 1 and two patients in arm 2. Using the immune-related RECIST criteria (irRC), arm 2 had an additional patient with SD for 81 weeks. Immune-related response criteria (irRC) account for the kinetics of both old and new lesions given the known potential delayed responses with IPI. The quality of the responses in the two arms was different. Patients with SD on arm 1 had continuous disease progression that did not reach the 20% growth cutoff for 7 and 22 weeks. Arm 2 had three SD responses (one patient demonstrated a regression starting at week 14 that was maintained until week 31, another patient's disease stabilized starting at week 22 and was maintained for 81 weeks,

and the third SD was maintained for 71 weeks while that patient was on study). The second patient initially received GVAX as a participant in the above mentioned neoadjuvant and adjuvant vaccine study. After he had recurrence, he received additional chemotherapy and radiation therapy, but continued to have disease progression. Later, when we analyzed his tumor together with the other PDA tumors from the neoadjuvant and adjuvant vaccine study, we found that the lymphoid aggregates that formed in his surgically resected PDA showed an immune suppressive signature, characterized by a relatively high density of Foxp3+ cells, albeit high density of CD8+ cells, and relatively high expression of CTLA-4. However, after he received the combination of IPI and GVAX treatments, even after he had an early local progression and developed a new omental lesion at week 7 after beginning the combinatorial treatment, he had a delayed, albeit durable disease stabilization starting at week 22. Four years after recurrence, this patient is still alive and is 2 years out from his last treatment. Although his CT scan still showed soft tissue density in the local pancreatic region and peritoneal nodularity, biopsy of these lesions failed to demonstrate malignant cells. This data, albeit anecdotal, suggests that the combination of checkpoint inhibitor and vaccine therapies may reverse an unfavorable TME that is dominated by immune suppressive signals and allow for the generation of a productive antitumor response. Nevertheless, IPI was associated with high grade including immune-related adverse events (irAE); thus, a checkpoint inhibitor such as anti-PD-1 therapy that is associated with less frequent irAE and has the same efficacy as IPI has gained much interest.

4.2.6 *The J0810 study of neoadjuvant and adjuvant GM-CSF allogeneic vaccine alone and given in sequence with immune modulating doses of IV or oral Cyclophosphamide in subjects with resectable pancreatic cancer*

Between July 2008 and September 2012, 59 patients were enrolled into a study (NCT00727441, J0810) of an irradiated, allogeneic GM-CSF-secreting pancreatic tumor vaccine (GVAX) administered intradermally either alone or in combination with immune modulatory doses of cyclophosphamide (Cy) as neoadjuvant and adjuvant treatment for patients with resectable PDA. The immune modulatory role of low dose Cy in depleting regulatory T cells were demonstrated in a number of pre-clinical and clinical studies [26–33]. Most of these 59 patients were enrolled during a 24-month active enrollment period. Patients were randomized 1:1:1 to 3 treatment arms [34]. In Arm A, patients received GVAX alone; in Arm B, patients received GVAX plus a single intravenous dose of Cy at 200 mg/m2 1 day prior to each vaccination; in Arm C, patients received GVAX plus oral Cy at 100 mg once daily for 1 week on and 1 week off. Up to 6 GVAX treatments were administered and all of the patients remained in their initial treatment arms throughout the duration of the study. All 59 of the patients received the 1st GVAX treatment 2 weeks +/- 4 days prior to surgery. Fifty-four (92%) patients successfully underwent pancreaticoduodenectomy (the Whipple surgery) and received the 2nd GVAX treatment. Eligible patients must have a mass in the head, neck and uncinate process of the pancreas suspected for adenocarcinoma by a multidisciplinary clinical trial team comprised of radiologists, surgical oncologists and medical oncologists. Biopsy would not be routinely required prior to surgical resection of a mass of pancreas suspected for PDA; therefore, biopsy was also not required at the entry of this vaccine study. Five patients were found intraoperatively to have liver metastases, which were not radiographically identified prior

to surgery, and instead underwent a bypass surgery. Among 54 patients who had pancreaticoduodenectomy, 1 patient was found to have ampullary cancer, 1 to have neuroendocrine tumor, 2 to have undifferentiated carcinoma, and 1 to have autoimmune pancreatitis. These patients' preoperative CT scans did not distinguish their disease process from PDA. In addition, 1 patient had grossly residual tumors and another 11 patients had recurrence immediately following the surgery. They were all taken off the study postoperatively. The 39 patients remaining on the study received standard adjuvant chemotherapy and radiation therapy. Patients remaining disease-free following chemoradiation therapy received up to 4 additional PDA GVAX treatments every 4 weeks.

This study demonstrated that it is safe to treat patients suspected to have PDA with pancreatic GVAX in the neoadjuvant setting, including patients who end up not having PDA. The sample size of this study was later increased to 90 in order to generate more preliminary data to support future research directions including the current application. Clinical outcome data in this study have not matured at the time of submitting this application. The study was not powered to compare the clinical efficacy analysis between arms; the primary focus was safety and immunologic correlates. We also do not anticipate that one additional vaccination in the neoadjuvant setting would significantly change patients' clinical outcome comparing to our prior study (clinical study J9988) of treating the patients with vaccines in the adjuvant setting [23] An interim preliminary analysis did show that the DFS and OS of patients in this neoadjuvant and adjuvant study is similar to our prior J9988 adjuvant vaccine study. More importantly, as described above and below, this neoadjuvant and adjuvant vaccine study has pioneered the neoadjuvant research approach for cancer immunotherapy and supported the use of the same neoadjuvant approach for the study of the combination of anti-PD-1 therapy and vaccine therapy.

Furthermore, the primary objective of that study was to analyze the effects of treatment on the TME. Pathologic examination of resected PDAs revealed the formation of vaccine-induced intratumoral tertiary lymphoid aggregates within two weeks following a single GVAX vaccine treatment, regardless of whether GVAX was combined with Cy or not. Gene microarray analysis of microdissected vaccine-induced lymphoid aggregates identified gene signatures representing five signaling pathways including the NF-kB, Treg/TH17, chemokine, integrin/adhesion, and ubiquitin-dependent proteosome pathways. Gene expression and immunohistochemistry analyses further demonstrated that the Treg pathway is suppressed and the TH17 pathway is enhanced in lymphoid aggregates from patients who survive more than 3 years, in patients who demonstrate vaccine-enhanced mesothelin-specific T cell responses, and in patients with increased Teffector/Treg (CD8/Foxp3) ratios in their tumors. Overall, this study showed for the first time that GVAX-based immunotherapy can convert an immunologically inactive TME into an immunologically active TME; and that GVAX induces the formation of intratumoral tertiary lymphoid aggregates that facilitate a TH17-dominated anti-cancer response within the PDA TME following immunotherapy treatment.

The primary objective of the study described above is to compare IL17 expression in vaccine-induced lymphoid aggregates between resected PDAs from patients treated with the combination of GVAX/Cy and anti-PD-1 antibody vs. GVAX/Cy alone. Our prior studies showed that higher IL17A expression in lymphoid aggregates was associated with

longer OS in patients who received neoadjuvant and adjuvant GVAX (Figures 4-6, Lutz et al. [34]). This is the strongest biomarker identified through this prior study. Published studies have suggested that PD-1 blockade enhances TH17 response in patients with melanoma and prostate cancer. Therefore, we hypothesize that anti-PD-1 therapy will enhance IL17A expression in vaccine induced lymphoid aggregates. We are also going to analyze other immune parameters as part of explorative endpoints.

Consistent with the induction of an adaptive immune response, treatment with GVAX induced interferon gamma (IFN-y)-production in Teffs infiltrating PDAs, but also induced the upregulation of immunosuppressive regulatory mechanisms, including upregulation of the PD-1/PD-L1 pathway[34]. At baseline, only a small fraction of PDA epithelial tumor cells express low levels of membranous PD-L1. By contrast, GVAX therapy induced moderate expression of membranous PD-L1 on the epithelial tumor cells, and also induced the infiltration of innate immune cells expressing high levels of PD-L1 into the intratumoral lymphoid aggregates (see ***Figure 2***) [34]. PD-L1 expression may be regulated by oncogenic pathways. However, in most cancers, PD-L1 is induced by cytokines produced by infiltrating immune cells during the induction of an adaptive immune response, such as IFN-y [34]. In melanoma, NSCLC and renal cell carcinoma, PD-L1 expression by tumor cells has been observed in approximately 53-89% of untreated patients' tumors and by tumor infiltrating immune cells in approximately 50-100% of tumors [35]. PD-L1 expression by both tumor cells and tumor infiltrating immune cells in untreated patients with these cancers is associated with PD-1 expression in tumor infiltrating lymphocytes (TILs), more abundant infiltration of immune effector cells, and the presence of lymphoid aggregates. The high prevalence of immune cell infiltration and PD-L1 expression in these particular malignancies may explain their relatively high response rates to single therapy with anti-PD-1 or anti-PD-L1. By contrast, PDA demonstrates a minimal response to anti-PD-1/PD-L1 single therapies that is likely due to the absence of immune effector cell infiltration and low PD-L1 expression in vaccine-naïve PDAs. However, we hypothesize that by inducing immune cell infiltration and PD-L1 expression in the TME, GVAX therapy primes the PDA TME for anti-PD-1/PD-L1 therapies. Therefore, in this application, we will test this hypothesis through a novel clinical trial designed to test the combination of GVAX and anti-PD-1 antibody in both neoadjuvant and adjuvant settings in patients with resectable PDA.

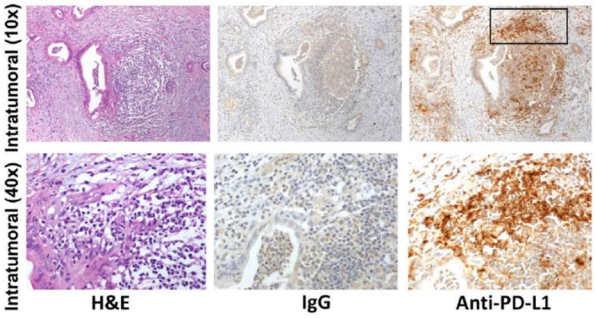


Figure 2 *(from Lutz et al.[34]): GVAX therapy induces the infiltration of innate immune cells expressing high levels of PD-L1 into the intratumoral lymphoid aggregates. Here, a representative intratumoral lymphoid aggregate from a vaccine-treated patient with pancreatic ductal adenocarcinoma is shown. This supports the hypothesis that vaccine-based therapies can convert a "non-immunogenic" neoplasm into an "immunogenic" neoplasm that may be sensitive to immune checkpoint inhibitors.*

4.3 Rationale

A multi-institutional study of BR-PDAC is now justified and appropriate given the following considerations: First, the optimal management of BR-PDAC remains undefined. Second, the recent publication of national "consensus statements" regarding BR-PDAC has provided a definition through which this disease can be studied, and reflects a growing interest in serving this unique patient population. Third, the prognosis for BR-PDAC with current approaches to therapy remains poor and novel approaches to treating these patients are needed.

A strong rationale exists for the use of preoperative therapy followed by surgery in patients with BR-PDAC, because upfront surgery in these patients results in a high probability of incomplete resection, and the prognosis of resected pancreatic cancer is highly dependent on margin status. The reported results of the Alliance A021101 trial, which utilized the preoperative regimen of FOLFIRINOX and chemoradiation (CRT), provide initial support for neoadjuvant therapy in BR-PDAC [12]. However, the results of this leave significant room for improvement; objective responses were uncommon and only 9% of patients achieved a pathologic CR.

Importantly the use of preoperative chemoradiotherapy in patients with BR-PDAC, has also been shown to promote infiltration of CD8+ T Cells into the TME of PDAC. Additionally, among the patients who received neoadjuvant chemoradiotherapy those with higher accumulation of CD8+ experienced a longer survival as compared to those who had lower CD8+ T cell infiltration. [36] This is consistent with our own experience in patients with borderline or locally advanced PDAC, who received neoadjuvant chemoradiotherapy. In these patients we appreciated that higher CD8+ infiltration relative to immunosuppressive T reg cells correlated with both improved local progression free survival and overall survival (figure 3).

The present study builds upon the Alliance A021101 trial, our experiences and others with borderline resectable pancreatic cancer, by taking advantage of a number of recent advancements in pancreatic immunotherapy and radiation therapy. Initially, patients will be treated with FOLFIRINOX, a regimen that is highly effective for metastatic PDAC[5,37] and appears to be effective in the preoperative setting on the basis of the Alliance study [12]. The goal of the chemotherapy is not only to reduce the size of the primary pancreatic lesion, but also to eliminate micrometastatic disease that might be present, and to reset the immune system. Although the appropriate sequencing of chemotherapy and immunotherapy in diseases where both therapies are known to be active remains unclear, there is emerging evidence that chemotherapies can modulate the host immune system through the expression of cancer neoantigens and in other ways that are just starting to be understood.

After chemotherapy, patients will be treated with Cy/GVAX/nivolumab immunotherapy. As discussed above, preclinical and clinical research conducted at Johns Hopkins has shown that the GVAX vaccine, either alone or in combination with immune modulating doses of Cy to deplete regulatory T cells, can have profound effects on the tumor microenvironment. Pathological examination of PDA tumor tissue resected just two weeks following a single neoadjuvant dose of GVAX identified the formation of novel vaccine-induced, immunologically active, tertiary lymphoid aggregates, organized lymph node-like structures that are not observed in tumor tissue resected from unvaccinated patients. However, activated T cells secrete interferon-gamma, which in turn upregulates the PD-1/PD-L1 pathway. Therefore, in this protocol, we have combined Cy/GVAX with a PD-1/PD-L1 pathway inhibitor (nivolumab) in order to prevent immune escape.

Finally, the immunotherapy will be administered concurrently with SBRT, an important recent advance in the treatment of localized pancreatic cancer. While studies using

conventional chemoradiation for non-metastatic pancreatic cancer have had conflicting results, SBRT is a contemporary form of RT that involves a short course of radiation delivered at a higher dose than conventional RT. Studies of SBRT have been encouraging and suggest that it can cause tumor regression away from involved vasculature, thereby improving the chances of negative surgical margins. Importantly, because the radiation course is short, the potential for delay of definitive surgery is reduced. Additionally, shorter courses of radiation may be immunologically preferential, resulting in acute rather than chronic antigen exposure and thereby reducing T cell anergy, exhaustion, and senescence. In this study, radiation has been combined with immunotherapy (Cy/GVAX/nivolumab) because of emerging evidence of synergy between these treatment modalities. Through the killing of tumor cells, radiation can stimulate antigen-specific CD8+ T cells through the presentation of antigen, thereby potentiating antitumor immune responses with Cy/GVAX/nivolumab.

5. PATIENT SELECTION

5.1 Eligibility Criteria

5.1.1 Histologically confirmed pancreatic adenocarcinoma* that is borderline resectable. Borderline resectable is defined by the 2009 consensus statement issued by The Americas Hepatopancreatobiliary Association (AHPBA)/Society for Surgery of the Alimentary Tract (SSAT)/Society of Surgical Oncology (SSO)/National Comprehensive Cancer Network (NCCN):

- venous involvement of the SMB/PV demonstrating tumor abutment, encasement, or short segment venous occlusion, but with suitable vessel proximal and distal to the area of vessel involvement, allowing for safe resection and reconstruction

OR

- gastroduodenal artery encasement up to the hepatic artery and short segment encasement/direct tumor abutment of the hepatic artery with no extension to the celiac axis

OR

- tumor-SMA involvement <180 degrees

*Pancreatic adenocarcinoma with squamous features is considered pancreatic adenocarcinoma (malignant squamous cells comprise <30%)

5.1.2 The patient has received no more than 1 month or 1 cycles (28 days) of systemic therapy for PDAC (prior symptomatic treatments such as pain medicines are acceptable). Patients receiving neoadjuvant chemotherapy who have not received more than 28 days or 1 month of therapy are eligible. The patient has not received any radiation therapy for PDAC.

5.1.3 Age >18 years

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

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

- White blood cell count ≥3,000/mcL
- absolute neutrophil count ≥1,500/mcL
- hemoglobin ≥ 9.0g/dl
- platelets ≥100,000/mcL
- total bilirubin ≤1.5 × institutional upper limit of normal
  - *Exception #1* Patients with an elevated bilirubin >1.5 x ULN due to biliary obstruction from PDAC may enroll if they have undergone an obstruction relieving intervention with at least 2 serial bilirubins decreasing
  - *Exception #2: Subjects with Gilbert syndrome may enroll as long as total bilirubin <3.0 mg/dL)*
- AST(SGOT)/ALT(SGPT) ≤5 × institutional upper limit of normal
  - **Note*: Patient's AST and ALT will need to be ≤3 x the upper limit of normal prior to the first cycle of immunotherapy
- serum creatinine ≤1.5 × institutional upper limit of normal
  OR
- creatinine clearance ≥40 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal if using the Cockcroft-Gault formula below):

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

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

5.1.6 Women of childbearing potential (WOCBP) must have a negative urine or serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]). WOCBP is defined in **Section 7.5**. NOTE: If a patient has a positive or indeterminate serum or urine pregnancy test, then an ultrasound must be done to rule out pregnancy to enroll on trial.

5.1.7 WOCBP must be willing to use either two adequate barrier methods or a barrier method plus a hormonal method of contraception to prevent pregnancy, or to abstain from heterosexual activity (complete abstinence) throughout the study, starting with visit 1 through 5 months after the last dose of study therapy. Approved contraceptive methods include, for example; intrauterine device, diaphragm with spermicide, cervical cap with spermicide, male condoms, female condoms with spermicide, or oral contraceptives. Spermicides alone are not an acceptable method of contraception. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

5.1.8 Male patients must agree to use an adequate method of contraception, or to abstain from heterosexual activity (complete abstinence), starting with the first dose of study drug through 7 months after the last dose of study therapy.

5.1.9 Patient must be a candidate for SBRT (Stereotactic body radiation therapy).

5.1.10 Patient must be willing to be treated with SBRT and have surgical resection (if eligible) only at the clinical trial site at which they are enrolled.

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

5.2 Exclusion Criteria

5.2.1 Patient has histologically confirmed squamous pancreatic cancer or adenosquamous pancreatic cancer with malignant squamous cells >30%

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

5.2.3 Patient has received or is receiving an investigational agent or used an investigational device for pancreatic cancer (or otherwise) within 28 days of the first dose of study drug.

5.2.4 Patients with a history of prior treatment with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA4 antibodies or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways.

5.2.5 Patient has completed more than 1 month or 1 cycle (28 days) of chemotherapy.

5.2.6 Has a diagnosis of immunodeficiency, is receiving systemic steroid therapy, or is receiving any other form of immunosuppressive therapy.

5.2.7 Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. Any patient bearing an allograft is not eligible.

5.2.8 Has a known additional histologically confirmed malignancy that is likely to be life-limiting in the opinion of the treating investigator, interfere with the evaluation of pancreatic cancer treatment response, or is likely to require treatment that would interfere with the treatment of the patient's pancreatic cancer. Superficial bladder cancer, non-melanoma skin cancers, or low grade prostate cancer not requiring therapy would not exclude participation in this trial.

5.2.9 History of allergic reactions attributed to compounds of similar chemical or biologic composition to agents used in study:

- Nivolumab
- Cyclophosphamide
- GM-CSF, hetastarch, corn, dimethyl sulfoxide, fetal bovine serum, trypsin (porcine origin), yeast or any other component of the GVAX vaccine.

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

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

5.2.12 Pregnant or breastfeeding.

5.2.13 Has a known diagnosis of human immunodeficiency virus (HIV), active tuberculosis (TB), active hepatitis B (e.g., HBsAg reactive) or hepatitis C (patients who are hepatitis C antibody positive may be enrolled if they have a confirmed negative viral load at screening).

5.2.14 Patient is on supplemental home oxygen.

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

5.2.16 Patient is, at the time of signing informed consent, a regular user (including "recreational use") of any illicit drugs or other substance abuse (including alcohol) that could potentially interfere with adherence to study procedures or requirements.

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

5.3 Inclusion of Women and Minorities

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

6. REGISTRATION PROCEDURES

6.1 General Guidelines

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

If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

6.2 Registration Process

To register a patient, the following de-identified documents should be completed by the Research Nurse or Study Coordinator and e-mailed to [redacted]

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

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

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

7. TREATMENT PLAN

7.1 Agent Administration

Treatment will be administered on an outpatient basis. Dosing delays are described in **Section 8.2**. After completing course of standard chemotherapy (2-8 cycles)

(FOLFIRINOX), subjects will receive two cycles of combined immunotherapy (nivolumab and Cy/GVAX). The combination immunotherapy should begin 2-4 weeks after last dose of FOLFIRINOX. Each cycle of combined immunotherapy consists of nivolumab and Cy on day 1, and GVAX on day 2, of a 21-day cycle. SBRT will be administered for 5 or 6 days concurrently with the start of the second cycle of combination immunotherapy. After receiving the first two treatments of immunotherapy, patients will be reevaluated for surgery. If eligible for surgery, they will undergo definitive resection. Following surgery (or if they do not receive surgical resection), they will resume standard of care management for their pancreatic cancer, which may consist of adjuvant chemotherapy.

Table 1: Study Regimen

Agent	***Premedications, Precautions***	***Dose***	***Route***
Cyclophosphamide	Subjects may be pre-medicated with anti-emetics	200 mg/m^2 in 100 mL NS	IV infusion over 30 minutes
GVAX	Lidocaine based topical anesthetic cream (approx 2.5gms/site at least 1 hour prior to vaccination)	5x10^8 cells	Six intradermal injections
nivolumab	No prophylactic pre-medications unless indicated by previous experience in an individual subject	240mg (flat dose)	IV over 60 minutes

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

Please see **Section 8.2** for guidance regarding dosing delays. In the case that a participant develops intolerance or side effect that is attributable to one agent (for example, intolerance only to nivolumab) during cycle 1 of immunotherapy, the participant may choose to continue treatment only with the other active agent(s) on study as otherwise indicated.

7.1.1 FOLFIRINOX

FOLFIRINOX is a standard treatment for PDAC, and treatment may be may be modified based on local treatment standards and guidelines as appropriate. FOLFIRINOX chemotherapy consists of 1) FOL – folinic acid (leucovorin), 2) F – fluorouracil (5-FU), 3) IRIN – irinotecan, and 4) OX – oxaliplatin. General recommendations for treatment with FOLFIRINOX are provided here (see Conroy et al. [5]). Patients who are unable to receive FOLFIRINOX or are intolerant to it may be switched to another standard chemotherapy regimen (gemcitabine/Abraxane [3]>) at the discretion of the patient's treating oncologist for the remaining portion of the standard chemotherapy portion of the study. Patients are considered to have completed the standard chemotherapy portion of the study when they have completed at least two 28-day cycles of FOLFIRINOX, or have completed at least two months of standard chemotherapy. It is recommended that patients receive four cycles of FOLFIRINOX but they may receive anywhere from two to eight cycles.

7.1.2 GM-CSF Vaccine

The vaccine consists of equal numbers (2.5 x 10^8 each) of Panc 6.03pcDNA1GM-CSF and Panc 10.05 pcDNA1/GM-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. Vaccine cells from each pancreas tumor cell line frozen at 1.25 x10^8 cells/vial (2 vials per cell line) in an injectable formulation (6% hetastarch, 2% human serum albumin, 5% dimethyl sulfoxide [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 upper 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.

7.1.3 Cy (Cytoxan^R)

The single intravenous (IV) dose of 200 mg/m^2 Cy is chosen based on our data showing that this single low IV dose given with a GM-CSF-secreting breast cancer vaccine is effective in reducing Treg levels in the PDA TME and facilitating enhanced T cell activation. Cy is a FDA-approved standard chemotherapy agent. Subjects may be pre-medicated prior to administration with anti-emetics per institutional guidelines. Subjects should be observed for a minimum of 30 minutes before administration of nivolumab. Acute reactions resulting in the delay of nivolumab will be managed using standard therapy for acute drug reactions as per institutional standard of care and reported to the IND Sponsor.

Dosing calculation based on weight:

The dosing calculations should be based on the body weight. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose, the dose must be recalculated

7.1.4 Nivolumab (OPDIVO ®, BMS-936558; MDX-1106)

This is a is a potent and selective monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, thereby releasing PD-1 pathway-mediated inhibition of the immune response, including anti-tumor immune response. It is FDA-approved for treating metastatic melanoma, metastatic non-small cell lung cancer (NSCLC), Hodgkin lymphoma, recurrent or metastatic squamous cell carcinoma of the head and neck, and kidney cancer. In this study, nivolumab will administered IV over 60 minutes at 240mg (flat dose). The drug can be diluted with 0.9% normal saline, USP or 5% Dextrose Injection, USP to protein concentrations as low as 1 mg/mL for delivery but the total drug concentration of the solution cannot be below 0.35 mg/ml. It is not to be administered as an IV push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline. Antiemetic medications should not be routinely administered prior to dosing except as indicated by patient's prior reaction. See **Section**

7.2.3.1 for subsequent premedication recommendations following a nivolumab-related infusion reaction.

7.1.5 SBRT and Fiducial placement

Fiducial Placement

1) Treatment on this protocol requires placement of 1-5 gold (99.9% pure, 1-5 mm length, visicoils, or other) fiducials for targeting purposes. The fiducials will be used as surrogates for visualizing and targeting the daily tumor position during treatment. The fiducials will be placed directly into the tumor and/or periphery under endoscopic ultrasound or CT guidance. Fiducials may be implanted prior to enrollment as this is an acceptable standard of care procedure for any patient receiving radiotherapy for pancreatic cancer. If a patient had an attempted surgical resection that was aborted, fiducials or surgical clips may have been implanted intraoperatively, which can subsequently be used if they can be sufficiently visualized during daily image guidance. If fiducials are not placed intraoperatively or prior to enrollment, placement will be done and is expected to be done on an outpatient basis. In rare occurrences when fiducials/clips cannot be placed, patients may be treated at the discretion of the PI.
2) If treatment is conducted on a linear accelerator with sufficient image guidance that allows daily visualization of target positioning without the need for fiducials (i.e. CT on rails or an MRI-guided linear accelerator), treatment without fiducials will be allowed.

SBRT Simulation

1) Simulation should be done following placement of fiducials; however, this may vary and is at the discretion of the principal investigator.
2) Typically, patients will be positioned supine in an Alpha Cradle, Vac-loc, or equivalent immobilization device that will be custom-made for each patient.
3) Patients should fast at least 2 hours prior to CT simulation, and similar instructions should be given at the time of treatment. Specific instructions regarding duration of fasting will be left to the discretion of the treating radiation oncologist and will be individualized to the patient.
4) IV should be used for simulation, unless the patient has renal insufficiency or an iodine allergy. Oral contrast may also be used for small bowel visualization. MRI simulation can also be performed to assist in target delineation.
5) Motion management can be addressed using respiratory gating, breath-hold, abdominal compression, and/or respiratory tracking. Specific motion management decisions will be made by the treating radiation oncologist.
6) Simulation CT slice thickness must be no greater than 3mm.
7) As long as the specified dosimetric parameters for SBRT are reached, patients may be treated on any IGRT-enabled machine.
8) All patients must start Linac based SBRT within 4 weeks of the simulation scan.

SBRT Treatment Planning

1) An SBRT treatment plan will be developed using the preferred institutional treatment planning system. Institutional standards for radiation quality assurance and radiation delivery will be utilized.
2) The gross tumor volume (GTV) will consist of the primary tumor, as defined on all available contrasted diagnostic imaging (CT/MRI/PET), along with CT simulation scan.
3) Consideration will also be given to include the following, either in the GTV or a separate clinical tumor volume (CTV)
    A. The full circumference of involved vasculature
    B. Suspicious regional nodes (greater than 1.0cm or other suspicious features)
    C. The initial extent of disease involvement prior to initiation of chemotherapy
    D. At-risk elective nodal basins such as the celiac, SMA, SMV, PV, and para-aortic nodal basins (Dholakia et al., IJROBP, 2013), particularly if there is concerning stranding or other suspicious features on imaging.
4) Decisions regarding target coverage will factor in the ability to safely meet dose constraints.
5) Depending on the motion management strategy employed, subsequent volumes and margins will be constructed. For free-breathing treatment, an internal tumor volume (ITV) will be constructed to reflect the volume through which the target moves with respiration. For active-breathing control, multiple CT scans may be taken at the time of simulation to understand reproducibility of this approach. A planning tumor volume (PTV) will be further created to capture additional uncertainty in patient positioning during and between treatments. The PTV margin will depend on the specific clinical circumstances, but will likely be on the order of 2-5mm.
6) Critical structures to be contoured include the stomach, duodenum, bowel, left and right kidneys, liver, and spinal cord. Separate contours can be created for large and small bowel. Radiation dose to the adjacent normal tissue will be minimized. Dose constraints to be used include:
    A) Stomach: required: V33<1cc; recommended: V20<20cc
    B) Duodenum: required: V33<1cc; recommended: V20<20cc
    C) Other small bowel: required V33<1cc; recommended V20<20cc
    D) Large bowel: required V33<1cc; recommended V20<20cc
    E) Liver: 50% should be limited to <12 Gy
    F) Right Kidney: V12<25%
    G) Left kidney: V12<25%
    H) Spinal cord: max dose <8 Gy
7) Coverage of target volumes (i.e. GTV, CTV, ITV, PTV, etc.) with 25 Gy and 33 Gy isodose lines will be assessed
    A) If coverage is poor due to dose constraints, the radiation oncologist may decide that the patient is a poor candidate for SBRT. A minimum of 100% of coverage of the GTV with 25 Gy must be achieved to be eligible for the protocol.
8) Contours of the fiducials used for target localization will be generated on the applicable image sets, to be used for patient set-up on treatment.

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

SBRT Treatment Delivery

7) Patients will receive 5 fractions of 6.6 Gy delivered over consecutive business days, as delineated above. Ideally, all 5 fractions should be delivered Monday through Friday; however, treatment may be delivered over 2 weeks, as long as the patient receives at least two fractions per week.
8) Daily treatment set-up will include the following steps:
   A) Patients should be positioned as in the simulation
   B) Volumetric image-guidance will be employed to align the patient, initially to bony landmarks, follow by a shift to the tumor/fiducials
   C) Target, OAR, PRV, and isodose line structures can be sent to the machine to allow assessment of daily dose deposition and any additional shifts required or whether it is safe to proceed with treatment.
   D) Intra-fraction image guidance can be assessed to allow intra-fraction adjustment of positioning

7.1.6 Definitive Surgical Resection

Following the interventions/treatments above, patients who are determined to have resectable disease will undergo a definitive surgical resection. The surgical procedure performed will result in either a R0, R1 or R2 resection as determined by the operating surgeon.

7.2 General Concomitant Medication and Supportive Care Guidelines

7.2.1 Cyclophosphamide (Cy)

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

7.2.2 GVAX Pancreas Vaccine

Local vaccine site reaction may be treated with topical applications of aloe vera or vitamin E gel or lotion. Significant local inflammation that is causing the subject severe pain or is interfering with the activities of daily living may be treated with oral analgesics. Local toxicities of pruritus at the vaccine sites and systemic pruritus may be treated with topical or oral diphenhydramine hydrochloride (Benadryl®) or topical aloe vera. If oral diphenhydramine hydrochloride is used the recommended dose shall be 25-50 mg every four to six hours as needed for pruritus, not to exceed 300 mg/day. Cases of local ulceration should be manageable with local wound care, with or without antibiotics. Severe local inflammation or significant clinical autoimmunity will be managed on a case-by-case basis.

7.2.3 Nivolumab

Nivolumab is a fully human monoclonal immunoglobulin (Ig) G4 antibodies. Subjects should be closely monitored for potential AEs during antibody infusion and potential AEs

throughout the study.

7.2.3.1 Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce an infusion or hypersensitivity reaction. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All grade 3 or 4 infusion reactions should be reported within 24 hours to the IND Sponsor and BMS as an SAE if the criteria are met. Infusion reactions should be graded according to CTCAE (version 4.03) guidelines. Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as appropriate:

For Grade 1 symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated)

Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional nivolumab administrations.

For Grade 2 symptoms: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [e.g, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for 24 hours).

Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further nivolumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms: (Severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]). Grade 4: (life threatening; pressor or ventilatory support indicated).

Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

Please refer to **Section 8.2** for guidelines regarding GVAX treatment delays following a nivolumab infusion-related reaction.

7.2.3.2 Nivolumab-Related Adverse Events

Blocking PD-1 function may permit the emergence of auto-reactive T cells and resultant clinical autoimmunity. Rash/pruritus, diarrhea/colitis, pneumonitis, hepatitis, and hypothyroidism were drug-related, presumptive autoimmune events noted in previous nivolumab studies.

For the purposes of this study, a nivolumab-related AE 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. Serological, immunological, and histological (biopsy) data should be used to support the diagnosis of an immune-mediated toxicity. Suspected nivolumab-related AEs must be documented on an AE CRF. Identification and treatment of nivolumab-related AEs can be found in **Appendix B**. Additional guidance can be found in the nivolumab Investigator's Brochures (IB).

7.3 Prohibited and Restricted Therapies

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

- Any non-study anticancer or immunotherapy agent (investigational or non-investigational)
- Any other investigational agents
- Systemically active steroids can be used but should be reported to the Principal Investigator and IND Sponsor. Steroid treatment should be completed at least 14 days prior to resuming study-related treatments unless approval to resume sooner is obtained from the IND Sponsor (See **Section 8.2** for dosing delays for steroids)
- Filgrastim (Neupogen® or G-CSF) or sargramostim (Leukine® or GM-CSF)
- 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.

- The use of anticoagulants is known to increase the risk of gastrointestinal hemorrhage. Since gastrointestinal hemorrhage is an adverse reaction with nivolumab, subjects who require concomitant anticoagulant therapy should be monitored closely.

7.4 Definition of an Overdose for this Protocol

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as SAEs.

7.5 WOCBP, Contraception, Use in Pregnancy, Use in Nursing:

7.5.1 WOCBP

A WOCBP is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes.

7.5.2 Contraception

The investigational agents used in this protocol may have adverse effects on a fetus in utero. Furthermore, it is not known if the investigational agents have transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 2 years will be considered postmenopausal), or 3) amenorrheaic for <2 years without a hysterectomy and oophorectomy and with a documented FSH value in the postmenopausal range, or 4) not heterosexually active for the duration of the study, or 5) heterosexually active and willing to use 2 methods of birth control (which is also required for the female partners of male subjects). The 2 birth control methods can be 2 barrier methods or a barrier method plus a hormonal method to prevent pregnancy, used throughout the study starting with Visit 1 through 5 months after the last dose of study medication. Male subjects enrolled in this study must also agree to use an adequate method of contraception starting with Visit 1 through 7 months after the last dose of study drug.

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% per year when used consistently and correctly.

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

- Male condoms with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants, and intrauterine devices (IUDs) such as Mirena by WOCBP subject or male subject's WOCBP partner.
- Nonhormonal IUDs, such as ParaGard
- Vasectomy
- Complete abstinence

Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Abstinence is only acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

LESS EFFECTIVE METHODS OF CONTRACEPTION

- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal sponge
- Male condom without spermicide*
- Progestin only pills by WOCBP subject or male subject's WOCBP partner
- Female condom*

*A male and female condom must not be used together

Subjects 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 subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

7.5.3 Use in Pregnancy

The investigational agents used in this protocol may have adverse effects on a fetus; therefore, women with a positive pregnancy test at screening will not be eligible for enrollment. If a subject inadvertently becomes pregnant while on treatment, the subject will immediately be removed from the study treatment. The study team will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated.

The investigator must immediately notify the IND Sponsor and BMS of any pregnancy using the Pregnancy Surveillance Form within 24 hours of notification and in accordance

with the SAE reporting procedures described in **Section 9.5**. Any pregnancy that occurs in a female partner of a male study participant should also be reported to the IND Sponsor and BMS.

Protocol required procedures for study treatment discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

7.5.4 Use in Nursing Women

Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

7.6 Nivolumab Treatment Discontinuation

Permanent discontinuation of study treatment should be considered for any of the following:

1. Severe or life-threatening related AEs, including, but not limited to, any of the following (the IND Sponsor and BMS must be notified in the event of these AEs):
    - Any grade 2 treatment-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks of starting therapy OR requires systemic treatment
    - Any grade 3 non-skin, drug-related AE lasting > 7 days, with the following exceptions:
        - Grade 3 treatment-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
        - Grade 3 treatment-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
        - Grade 3 treatment-related laboratory abnormalities do not require treatment discontinuation except:
            - Grade 3 treatment-related thrombocytopenia > 7 days OR that is associated with bleeding requires discontinuation
            - Any treatment-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
                - Total bilirubin > 5 × ULN

- Concurrent AST or ALT > 3 × ULN **and** total bilirubin > 2 × ULN

- Any grade 4 treatment-related AE or laboratory abnormality, except for the following events which do not require discontinuation:
  - Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations, or radiographic signs of pancreatitis.
  - Isolated grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.
  - Grade 4 lymphopenia and leukopenia.
  - Grade 4 treatment-related endocrinopathy adverse events, such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the IND Sponsor.

7.7 Unacceptable Toxicities

Monitoring for unacceptable toxicities will occur during the experimental radioimmunotherapy portion of the study (initiation of SBRT plus Cy/GVAX/nivolumab until the Off Treatment Visit) and only toxicities probably associated with this therapy will be reported as an unacceptable toxicity (**Section 15.4**). Since FOLFIRINOX and surgery are a standard of care for this disease, toxicity commonly attributable to the FOLFIRINOX, surgery, or postoperative course will not be reported as an unacceptable toxicity. During this portion of the study, unacceptable toxicities are defined as:

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

Exceptions include:

- Asymptomatic amylase and lipase elevation
- Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.
- Grade 3 or 4 lymphopenia or leukopenia
- ≤ Grade 3 skin rash treated with steroids for less than 4 weeks
- ≥ grade 2 eye pain or reduction of visual acuity that does not respond to topical therapy and does not improve to ≤ grade 1 severity within 2 weeks of starting therapy, or requires systemic therapy is an unacceptable toxicity.
- Grade 3 endocrinopathies adequately controlled with only physiologic hormone replacement. Grade 4 endocrinopathy adverse events, such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement

(corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the IND Sponsor.

Unexpected Grade 3 or greater laboratory abnormalities should be repeated within 24-72 hours if clinically indicated and monitored as necessary to determine if the event meets the toxicity criteria. The proportion of unacceptable toxicities will be continuously monitored. See **Section 15.4** for details of toxicity monitoring.

7.8 Criteria for Removal from Treatment

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

- The patient or legal representative (such as a parent or legal guardian) withdraws consent for follow-up.
- Termination of the study
- 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:

- Development of distant metastatic disease
- The patient or legal representative (such as a parent or legal guardian) withdraws consent for treatment but not follow-up
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s) (see **Section 7.8**)
- Need for >2 dose delays due to the same drug-related toxicity as per the dose delay guidelines (see **Section 8.2**).
- If in the opinion of the Investigator, a change or temporal or permanent discontinuation of therapy would be in the best interest of the patient. The Sponsor should be included in this decision,
- Noncompliance with trial treatment or procedure requirements,
- Patient becomes pregnant. All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.
- Patient is lost to follow-up

In the case that a participant develops intolerance or side effect that is attributable to one agent (for example, intolerance only to nivolumab) during cycle 1 of immunotherapy, the participant may choose to continue treatment only with the other active agent(s) on study as otherwise indicated.

7.9 Off Study Treatment Visit

Patients are considered off study treatment beginning 60 days after surgical resection or after a decision not to resect has been made. Follow-up visits will be scheduled at the discretion of the patient's local oncologist and the results sent to us if the patient agrees. All attempts will be made to obtain disease-free and overall survival data on each patient.

A mandatory Off Study Treatment/Safety Follow-Up Visit should be performed approximately 30-60 days after surgical resection has been performed (or 30 days +/- 7 days after the last infusion of study medication in patients who are not a surgical candidate, or within 7 days prior to initiation of a new anti-cancer treatment, whichever comes first). All subjects will be followed for 30 days after their last dose of study drug for the development of AEs.

The patient will be monitored for adverse events up to the mandatory Off Study Treatment/Safety Follow-Up Visit or to resolution of toxicity to Grade 0-1, whichever occurs later. Surgical-related AEs will not be collected.

7.10 Duration of Follow Up

All subjects should continue to be monitored for disease status at the discretion of the treating oncologist. Subjects who complete or discontinue from treatment will be contacted (by phone or email) every three months (+/- 2 weeks) to monitor overall survival until 1) until death, 2) withdrawal of consent, or 3) study closure, whichever occurs first. Information of other cancer therapies after discontinuation from the study treatment will also be collected. In addition, SAEs that occur within 100 days (+14 day reporting window) of the end of treatment or before initiation of a new antineoplastic treatment should also be followed and recorded.

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.

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

- Detection of gene therapy-related delayed adverse events
- Documentation of all exposures to mutagenic agents and other medicinal products
- History, physical exam, or laboratory testing at minimum intervals of one year
- Documentation of any of the following:
  -New malignancy(ies)
  -New incidence or exacerbation of a pre-existing neurologic disorder
  -New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder
  -New incidence of a hematologic disorder

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

8. DOSING DELAYS/DOSE MODIFICATIONS

8.1 Dose Modifications

Dose modifications for the standard of care chemotherapy (eg FOLFIRINOX) is at the discretion of the treating medical oncologist. Dose reduction or dose increase of Cy, GVAX, and nivolumab will not be permitted in individual patients.

8.2 Dosing Criteria for the investigational immunotherapy agents

Dosing criteria for the standard of care chemotherapy (eg FOLFIRINOX) is at the discretion of the treating medical oncologist and is not be addressed in this protocol. This section pertains only to dosing criteria for the investigational immunotherapy.

Dosing for the investigational immunotherapy will be delayed for any of the criteria listed below:

- AST, ALT > 3.0 x ULN
- Total bilirubin >1.5 x ULN (for patients with diagnosed Gilbert's Syndrome, direct bilirubin should be within normal institutional limits)
- Hemoglobin < 8 g/dL
- ANC < 1000/uL
- Platelets < 80 x 103/uL

- Any ≥ Grade 2 non-skin, drug-related adverse event, with the following exception:
  - Grade 2 drug-related fatigue does not require a treatment delay.
  - Grade 2 hypothyroidism or thyroiditis
- Any ≥ Grade 3 skin, drug-related adverse event
- Any ≥ Grade 3 drug-related laboratory abnormality with the following exceptions:
  - Grade 3 lymphopenia does not require dose delay
  - Any Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay.
  - Isolated grade 3 or 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication

Subjects who require delay of nivolumab should be re-evaluated weekly or more frequently

if clinically indicated and resume nivolumab dosing when re-treatment criteria are met.

In order to standardize the management of AEs for all subjects, treatment management algorithms are included in **Appendix B**. Additional AE treatment management algorithms included in the nivolumab IB might be considered for individual cases.

Subjects may resume treatment with nivolumab when the treatment-related AE(s) resolve to grade ≤1 or baseline value, with the following exceptions:

- Subjects may resume treatment in the presence of grade 2 fatigue.
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin adverse event
- Treatment-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed.
- Treatment-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment, which include grade 2 hyperglycemia, hypothyroidism and thyroiditis.

8.3 Treatment Delays

Treatment delays for standard of care chemotherapy (eg FOLFIRINOX) are at the discretion of the treating medical oncologist. Patients are considered to have completed the standard chemotherapy portion of the study when they have completed two 28-day cycles of chemotherapy, or have completed at least two months of standard chemotherapy.

The first cycle of Cy, GVAX, and nivolumab should optimally be administered within two to four weeks of receiving the last dose of chemotherapy. However, if necessary due to resolving adverse events related to chemotherapy or any other reason, the first cycle of Cy/GVAX/nivolumab may be delayed by up to 2 weeks (i.e. AST/ALT are not below 3x ULN). If the first cycle of Cy/GVAX/nivolumab is delayed by more than 2 weeks, the Principal Investigator must be contacted for further instructions on continued treatment versus preceding to definitive resection.

The second cycle of Cy, GVAX, and nivolumab is to be administered approximately 3 weeks after the first cycle. If the second cycle is delayed by more than 1 week, the Protocol Chair must be contacted for further instructions on continued treatment versus preceding directly to definitive resection. Additional delays or modifications to the treatment schedule must be approved by the Protocol Chair or the IND Sponsor.

SBRT should ideally be administered over five days or six days, beginning concurrently with cycle 2 day 1 of Cy/GVAX/nivolumab. An attempt will be made to schedule C2D1 on a Monday with a five-day treatment schedule, so that the patient may receive SBRT on a Monday-Friday schedule. If necessary, the start of SBRT may be delayed by up to 1 week, and can be delivered over 2 weeks, as long as the patient receives at least 2 fractions per week. Longer delays must be approved by the Protocol Chair. If cycle 2 day 1 of Cy/GVAX/nivolumab is delayed, SBRT should also be delayed to occur on the same day as the immunotherapy treatment.

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

- Nivolumab-related infusion reactions must resolve to baseline prior to administration of GVAX.
- Day 2 GVAX treatment and assessments can be resumed without repeating Day 1 study treatments (Cy and nivolumab) if the delay less than 72 hours.
- If the delay is longer than 72 hours and is in cycle 1, omit day 2 and proceed to cycle 2 with a minimum of 2 weeks from the previous Day 1 treatment. This includes steroid treatment requiring at least a 14-day washout prior to resuming study-related treatments.
- If the delay is longer than 72 hours and is in cycle 2, omit day 2 and proceed to definitive resection on study as otherwise indicated.

9. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

This study will use the descriptions and grading scales found in the revised National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 for adverse event reporting that can be found at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

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

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

9.1 Definitions

9.1.1 Adverse Event (AE)

An 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). The adverse event profile of the standard chemotherapy has already been well characterized. Therefore, adverse events occurring during the 2-8 cycles of standard chemotherapy portion of the study (before the initiation of the investigational agents, Cy/GVAX/nivolumab plus SBRT), 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.

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 (induce clinical signs or symptoms or require therapy).

9.1.2 Serious Adverse Event (SAE)

A serious adverse event is an undesirable sign, symptom or medical condition which:

- Results in death
- Is life threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see note below for exceptions) > 24 hours
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (note: reports of congenital anomalies/birth defects must also be reported on the Pregnancy Supplemental Form)
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above. Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- Is a new cancer (that is not a condition of the study)
- Is associated with an overdose
- Potential drug induced liver injury (DILI) is also considered an important medical event.
- Hemophagocytic lymphohistiocytosis is also considered an important medical event.
- Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.
- Is a pregnancy or pregnancy outcome of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, or stillbirth.

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

- Admissions as per protocol for a planned medical/surgical procedure or to facilitate a procedure
- Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)

- Medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).
- Admissions for monitoring of treatment-related infusion reactions that do not otherwise meet the criteria for a SAE.

9.2 Relationship and Grading

The relationship between the AE and the study treatment will be determined by the principal investigator.

- 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.

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 4.03) 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.

9.3 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.

9.4 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's Brochure (IB) and/or package inserts), and possibly, probably, or definitely related to CY, GVAX pancreas vaccine, or nivolumab. 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. Upon receiving such notices, the investigator must review and retain the notice with the IB 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.

9.5 Reporting

9.5.1 Adverse Events and Serious Adverse Events

All AEs (both expected and unexpected) will be captured on the appropriate study-specific CRFs. All adverse events experienced by subjects will be collected and reported from the first dose of the investigational agent (Cy/GVAX/nivolumab), throughout the study, and will be followed for 28 days after last dose of study drug unless related to the investigational agent. Adverse events that occur prior to the experimental treatment (i.e. during the standard chemotherapy portion of the study) will not be collected or reported. Subjects who have an ongoing adverse event related to the study drug(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. AEs that are an unacceptable toxicity will be reported to the IND Sponsor (Dr. Elizabeth Jaffee, e-mail: [redacted] **and** [redacted] within 24 hours once identified as such.

All SAEs (including deaths) occurring from the first dose of the study drug through 100 days (+ 14 day reporting window) after the last dose of nivolumab or within 7 days prior to initiation of a new antineoplastic treatment (whichever comes first) will be collected and reported. SAEs will be reported promptly to the IND sponsor (e-mail: [redacted] **and** [redacted] and BMS (e-mail: [redacted] within 24 hours of recognition of the SAE (**Appendix C)**. If this falls on a weekend or holiday, an email notification is acceptable but must be followed by an SAE reporting form on the next business day.

9.5.2 Follow-up of Adverse Events and Serious Adverse Events

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 regards 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 or dies

Once the event is resolved, the appropriate AE or SAE report page will be updated. The investigator will also ensure that the follow-up includes any supplemental information that may explain the causality of the event(s). New or updated information will be recorded on the originally completed AE or SAE report, with all changes signed and dated by the investigator or designee. The updated AE or SAE report will then be signed by the investigator and resubmitted to the IND Sponsor.

9.5.3 Reconciliation of SAEs

The Protocol Chair 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 GPVE will email, upon request from the Investigator, the reconciliation report. Requests for reconciliation should be sent to [redacted]
The data elements listed on the BMS GPVE reconciliation report will be used for case identification purposes. If the Sponsor determines a case was not transmitted to the IND Sponsor and/or BMS GVPE, the case should be sent immediately to the IND Sponsor and BMS.

9.5.4 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as SAEs.

9.5.5 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs. Potential drug induced liver injury is defined as:

- ALT or AST elevation > 3 times upper limit of normal (ULN)

AND

- Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)

AND

- No other immediately apparent possible causes of AST/ALT 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.

9.5.6 Pregnancy Reporting

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

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

All SAEs will be reported to the IRB and IBC per institutional standards. Follow-up information will be submitted to the IRB and IBC as soon as relevant information is available.

9.5.8 Food and Drug Administration (FDA)

All reporting to the FDA will be completed by the IND Sponsor.

9.5.8.1 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 (301-827-9796) to the FDA within 7 calendar days of first learning of the event. Follow-up information will be submitted to the FDA as soon as relevant information is available.

15 Calendar-Day Written Report:
The IND Sponsor is required to notify the FDA of any SAE that is unexpected and 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 included in the analysis. The new report should contain comments on the significance of the new event in light of the previous, similar reports.

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

9.5.8.2 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.

9.5.8.3 Recombinant DNA Advisory Committee (RAC)

Unexpected SAEs believed to be possibly related to the investigational product(s) will be reported to RAC by email if fatal or life-threatening within 7 calendar days or by written report if related and unexpected to the investigational product(s) within 15 calendar days. 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.

9.6 Special considerations for adverse events that occur during the surgery and postoperative course

Pancreatic surgery is one of the highest-risk procedures, requires prolonged hospitalization, has significant toxicities and is commonly associated with complications and comorbidities. It is a standard of care, therefore, is not part of this research study. From the day of surgery throughout the postoperative course day 30, participants will be primarily followed by their primary surgeons for monitoring and managing the complications and comorbidities attributable to the surgery. **Table 2** summarizes complications commonly associated with the pancreatic surgery based on several published analyses of more than 1000 patients at Johns Hopkins Medicines and other institutions. A normal, uncomplicated postoperative course is still commonly associated with laboratory abnormalities (grade1/2 AEs and occasionally grade 3 AEs) without needs of therapeutic interventions. At least one complication was associated with 58.5% of patients based on a recent analysis of a consecutive series of 633 patients undergoing pancreaticoduodenectomy at Johns Hopkins Medicine between February 2003 and August 2005. Grade I, II, III complications were common, in 10%, 30%, 13.5% of the patients, respectively. These complications and comorbidities are commonly associated with toxicities and laboratory abnormalities of CTCAE grade 3 and even grade 4. By contrast, Grade IV and V complications are relatively uncommon, in 3.0% and 2.0% of the patients, respectively (**Table 3**).

Table 2 Complications after Pancreaticoduodenectomy
Anastomotic leak, pancreas
Wound infection
Delayed gastric emptying
Hemorrhage, immediate postoperative or delayed
Intraabdominal abscess
Fascial dehiscence or evisceration
Supraventricular arrhythmia
Urinary tract infection
Anastomotic leak, biliary
Pancreatitis
Hypotension, shock
Cellulitis
Clostridium difficile colitis
Congestive heart failure, left ventricular dysfunction
Myocardial infarction
Renal failure
Apnea or hypoxia
Atelectasis
Catheter-related infection
Deep venous thrombosis
Dehydration
Anastomotic leak, intestinal
Gastrointestinal bleeding
Pleural effusion
Pneumonitis
Sepsis
Acute respiratory distress syndrome
Angina, cardiac ischemia
Aspiration
Cardiopulmonary arrest
Catheter-related infection
Constipation
Delerium tremens
Fever
Fluid imbalance
Gastroesophageal reflux disease
Congestive heart failure
Ileus
Interstitial pneumonitis and fibrosis
Prolonged intubation
Salivary gland infection
Small bowel obstruction

Table 3 Classification of Surgical Complication Adopted for Pancreatic Surgery

Grade	Definition
I	Any deviation from the normal postoperative course without pharmacologic treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.
II	Requiring pharmacologic treatment with drugs other than ones allowed for grade I complications. Blood transfusion and total parenteral nutrition* are also included.
III	Requiring surgical, endoscopic, or radiologic intervention
IIIa	Intervention not under general anesthesia
IIIb	Intervention under general anesthesia
IV	Life-threatening complication (including CNS complications)† requiring IC/ICU management
IVa	Single-organ dysfunction (including dialysis)
IVb	Multiorgan dysfunction
V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of the discharge, the suffix "d" (for disability) is added to the respective grade of complication (including resection of the pancreatic remnant). This label indicates the need for a follow-up to fully evaluate the complication.

*Note regarding DGE: The insertion of a central line for TPN or nasojejunal tube by endoscopy is a grade IIIa. However, if a central line is still in place or a feeding tube has been inserted at the time of surgery, then a TPN or enteral nutrition is a grade II complication.

†Brain hemorrhage, ischemic stroke, subarachnoidal bleeding, but excluding transient ischemic attacks.

CNS indicates central nervous system; IC, intermediate care; ICU, intensive care unit.

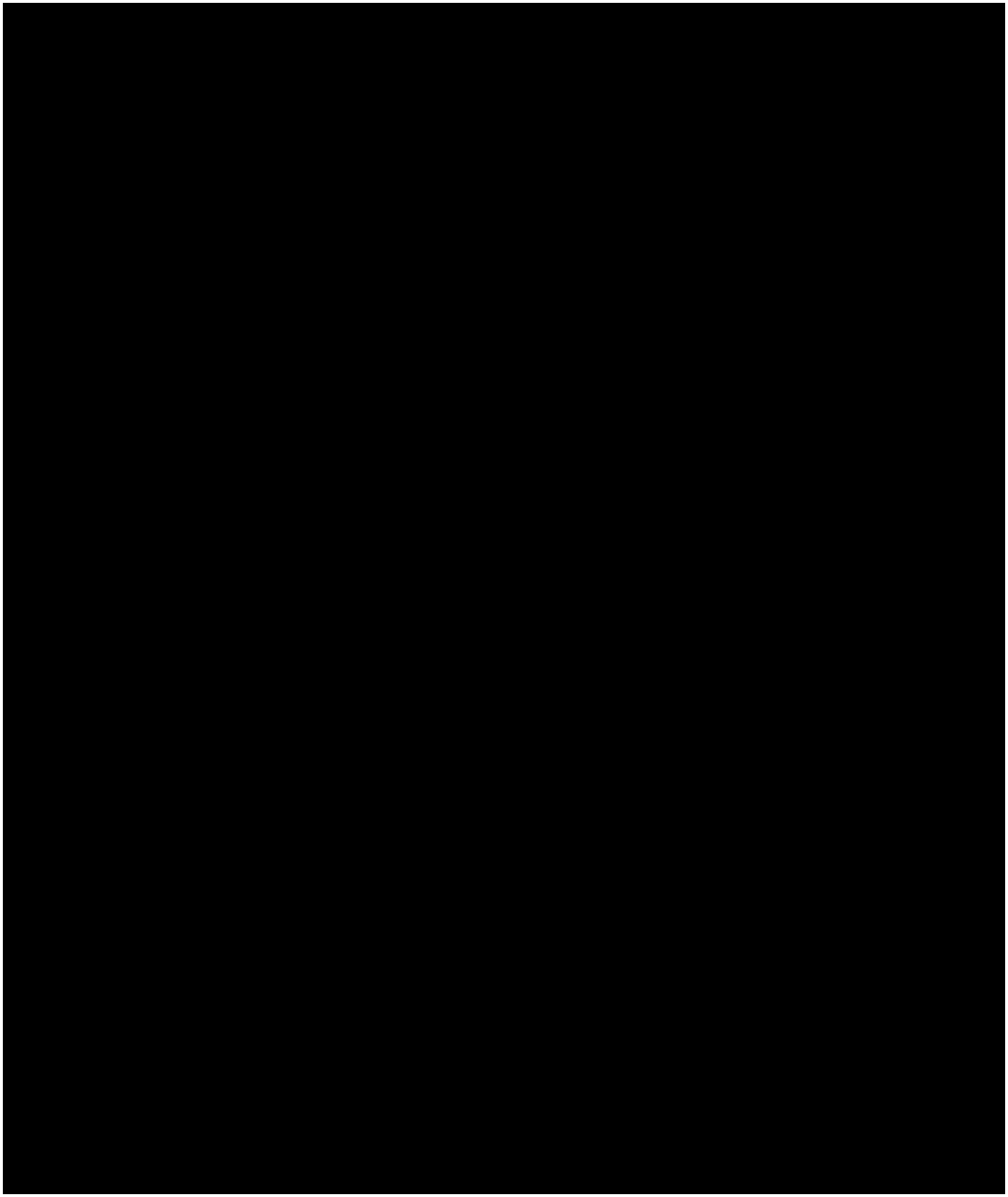
Pancreatic surgery is commonly associated with laboratory abnormalities in blood cell counts, serum electrolytes, liver function, and renal function, etc., with a range of severity from grade 1 to grade 4 by CTCAEv3.0 criteria. Grade I-III complications are common; therefore, laboratory abnormalities associated with a normal postoperative course or Grade I-III complications are considered to be within the commonly expected range of grades of severity (**Table 4**). Laboratory abnormalities beyond these commonly expected ranges of severity should be considered uncommon. Although Grade IV and V complications have still occurred, any SAE including laboratory abnormalities associated with Grade IV/V complications should be considered uncommon.

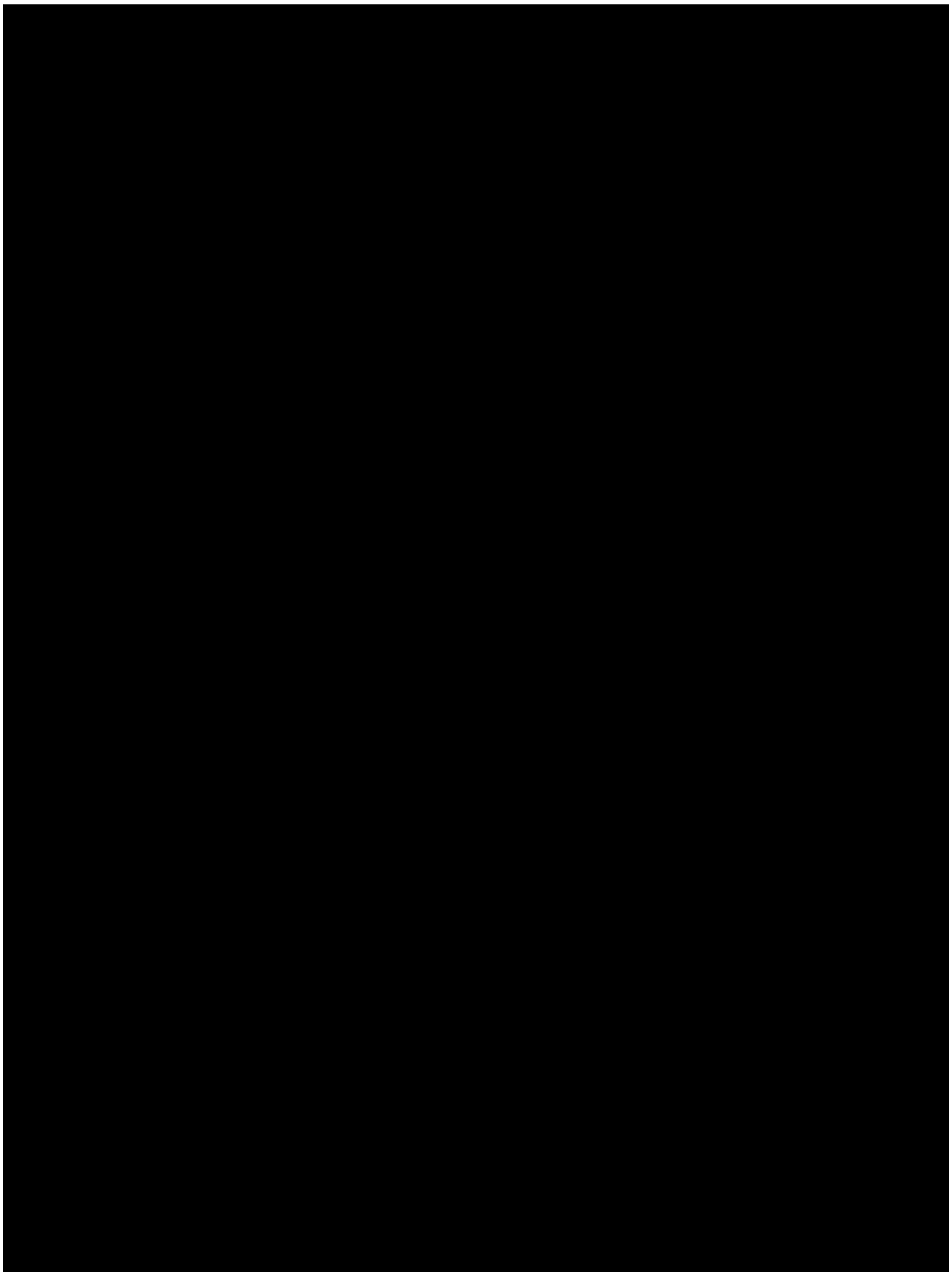
Table 4 Laboratory abnormalities commonly associated with pancreatic surgery

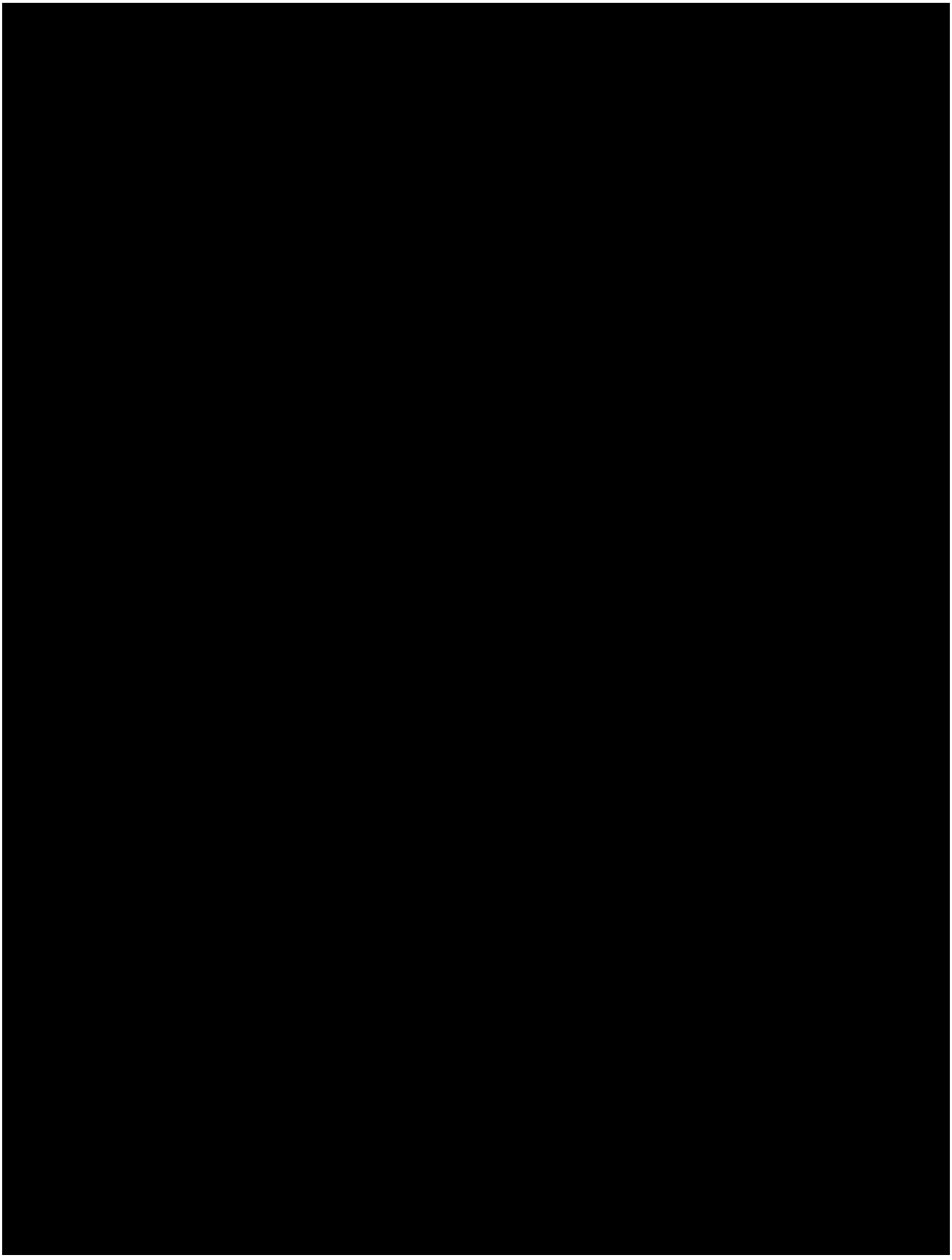
Lab test Abnormality	Ranges of severity by CTCAEv3.0 criteria	
Amylase	Elevated	Grade 1-4
Lipase	Elevated	Grade 1-4
Bilirubin	Elevated	Grade 1-4
AST	Elevated	Grade 1-4
ALT	Elevated	Grade 1-4
Albumin	Decreased	Grade 1-3
Glucose	Elevated	Grade 1-4
Glucose	Decreased	Grade 1-4
Alk Phosphatase	Elevated	Grade 1-4
Creatinine	Elevated	Grade 1-3
Glomerular filtration rate	Decreased	Grade 1-3
Bicarbonate	Decreased	Grade 1-4
Acidosis	Increased	Grade 1-4
Alkylosis	Increased	Grade 1-4
CPK	Elevated	Grade 1-4
WBC	Elevated	Not graded by CTCAE
Hemoglobin	Decreased	Grade 1-3
Platelets	Elevated	Not graded by CTCAE
Platelets	Decreased	Grade 1-3
Sodium	Elevated	Grade 1-3
Sodium	Decreased	Grade 1-3
Potassium	Elevated	Grade 1-3
Potassium	Decreased	Grade 1-3
Magnesium	Elevated	Grade 1-3
Magnesium	Decreased	Grade 1-3
Phosphate	Elevated	Grade 1-3
Phosphate	Decreased	Grade 1-4
Calcium	Elevated	Grade 1-3
Calcium	Decreased	Grade 1-4

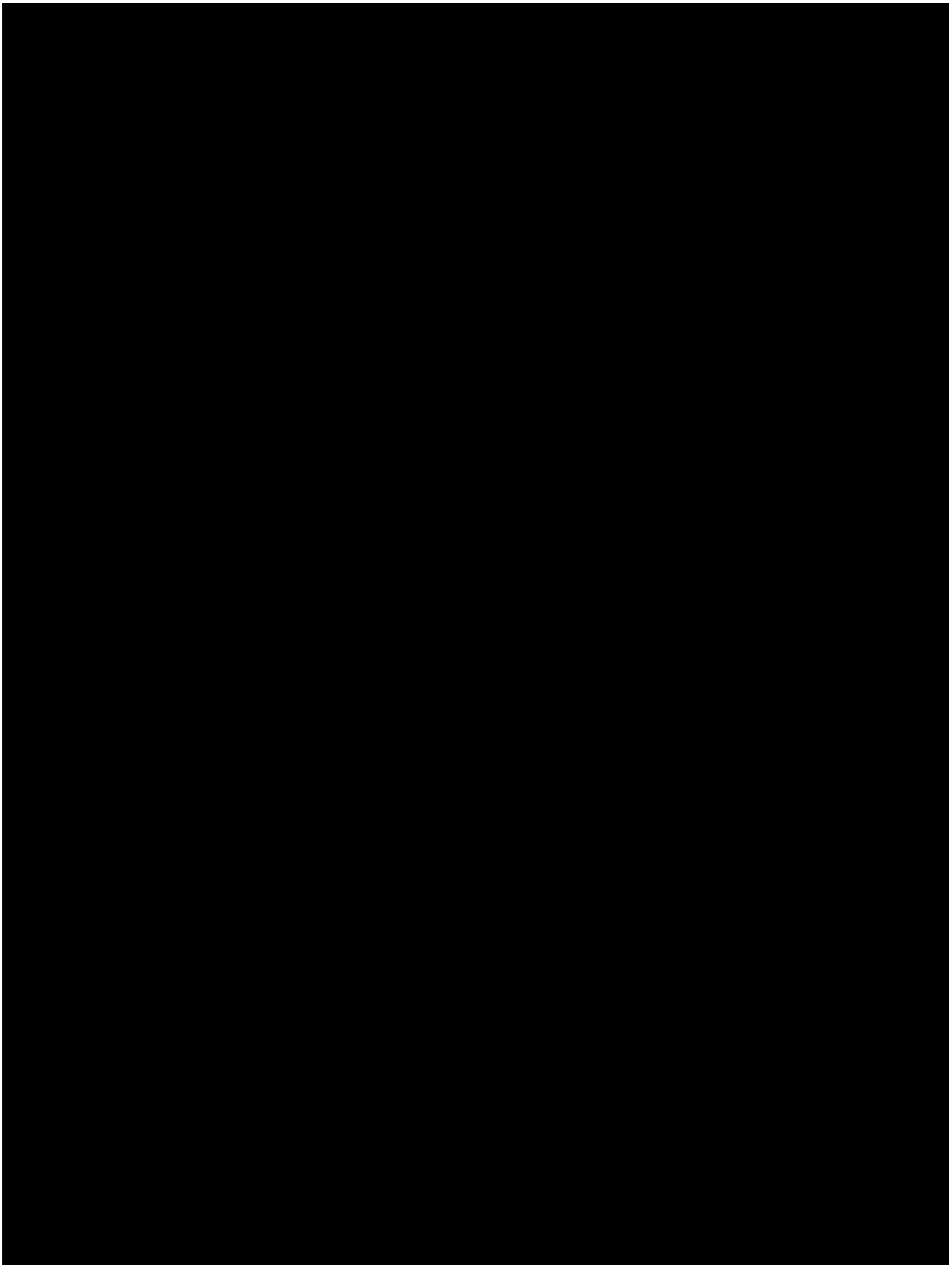
Therefore, during this period, first, the study will be focused on monitoring and reporting the complications with uncommon grades of severity such as Grade IV and Grade V complications by criteria used at Johns Hopkins (**Table 3**). The severity of any SAEs associated with such grades of complications should be considered uncommon. Second, any unusual complication not seen commonly with this operation will be reported. Third, the study will also be focused on monitoring and reporting any laboratory abnormality beyond the common ranges of severity (**Table 4**). Fourth, the study will also be focused on monitoring and reporting any type of toxicity not commonly attributable to the surgery or postoperative course. These events will be recorded as described in Section 9.1 and their severities will still be categorized by NCI CTCAEv4.0 criteria. Relationship of these events to the investigational drug will be determined by the principal investigator together with surgical co-investigators of the study team and, if necessary, with primary surgeons, and will be categorized as described in **Section 9**. Reporting of these events will follow the same guidelines described in **Sections 9.5**.

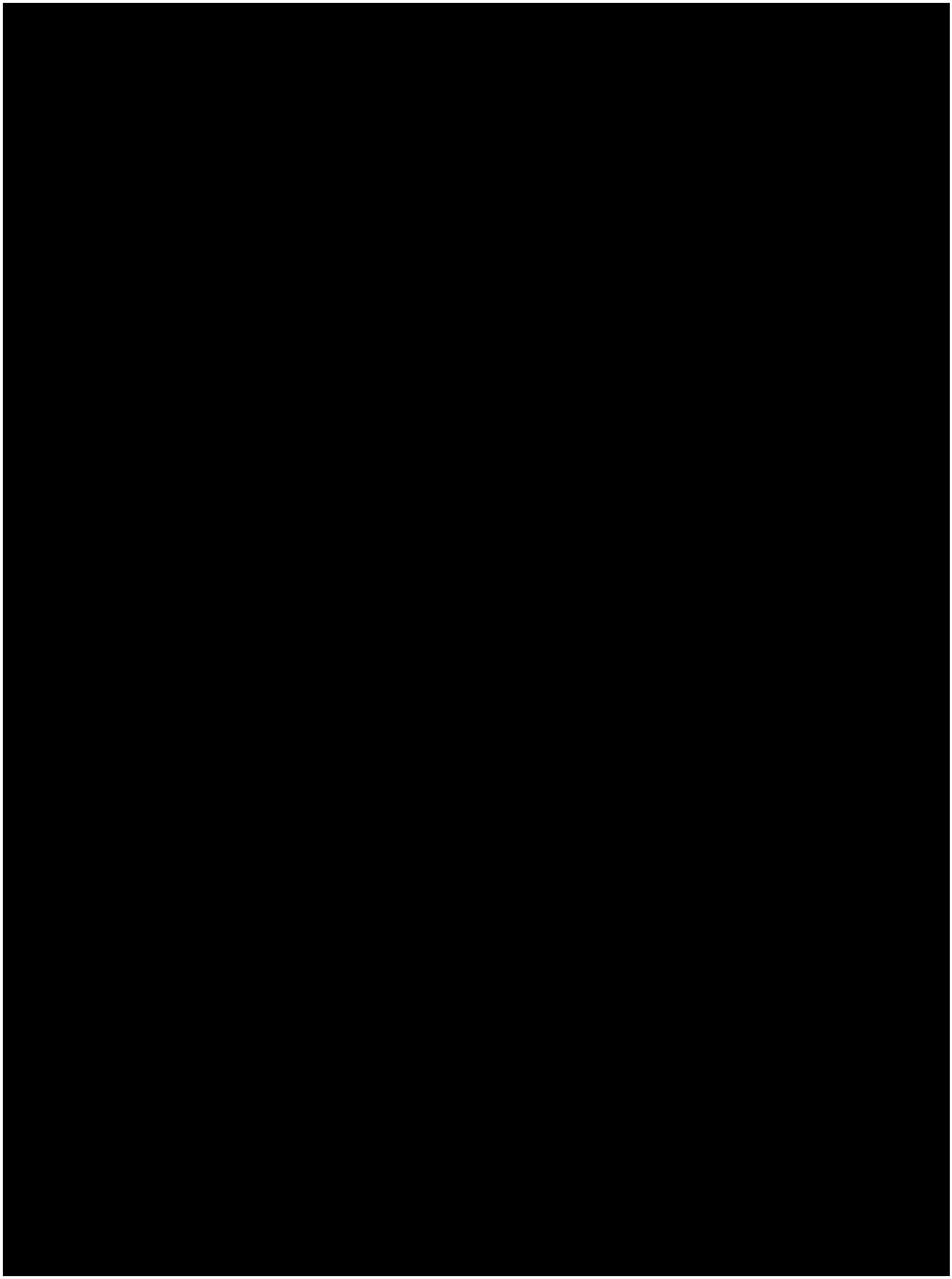
10. PHARMACEUTICAL INFORMATION

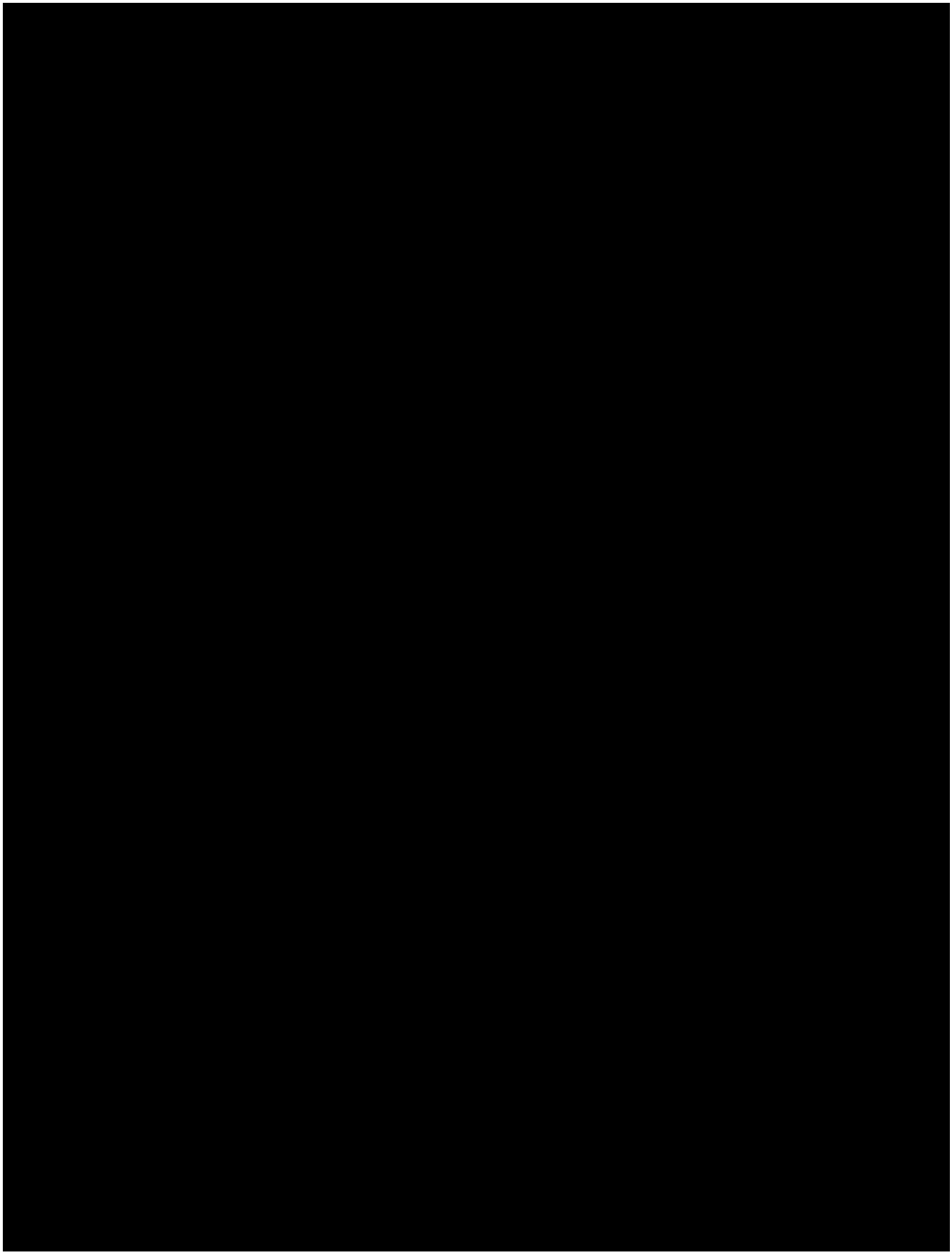












11. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

11.1 Tumor Tissue Studies

4-6 core tumor biopsies will be collected (if a subject's tumor is thought to be reasonably safe and easy to biopsy) during scheduled endoscopy with fiducial placement at select sites. Additional tissue will also be requested of patients after completion of 2 doses of combined immunotherapy and SBRT via surgical resection specimen, or intraoperative biopsy (if surgery is attempted but aborted). Archival tumor samples may also be collected for every patient (slides and/or blocks). Detailed instructions for tissue collection, processing, and shipment are provided in the Laboratory Manual.

The tissue samples will be banked for the evaluation of CD8+ T Cell effectors, MHC 1 expression, PD-L1 expression on tumor and PD-L1 on tumor-infiltrating immune cells, and their associated immune suppressive pathways and other immune activation pathways to assess the effect of treatment upon the tumor microenvironment and the correlations between these immune parameters and clinical response. Immunohistochemistry, flow cytometry, quantitative PCR assays and microarray analysis will be employed. In addition, to identify potential neoantigens as a result of radiation therapy, the banked tumor tissues will be used for whole exome sequencing (WES) to identify tumor-specific non-synonymous mutations. Peripheral Blood Lymphocytes (PBL) and tumor infiltrating lymphocytes (TIL), either directly from FFPE tumor sections, or following isolation, will be used for the TCR repertoire analysis by next-generation sequencing.

11.2 Whole Blood for Peripheral Blood Lymphocytes (PBLs)

Post-treatment expression of PD-1 and other lymphocyte activation markers will be measured and correlated with OS and DMFS. Whole blood for PBL will be collected with each immunotherapy and after completion of immunotherapy at select sites. Detailed instructions for blood collection, processing, and shipment are provided in the Laboratory Manual. 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).

11.3 Serum and Plasma Marker Studies

Sera and plasma will be collected at the time points detailed in the study schedule to identify potential therapeutic targets, biomarkers, and predictors of response and autoimmune toxicity. Detailed instructions for blood collection, processing, and shipment are provided in the Laboratory Manual.

11.4 Diagnostic Tissue Samples

Tissue, fluid, or blood may be collected from standard of care procedures used to treat or diagnoses immune related toxicities.

11.5 Genomic Analysis

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

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

12. STUDY SCHEDULE

1) Consent – Study consent should be obtained prior to the completion of one cycle (28 days) of standard of care chemotherapy for pancreatic cancer.
2) Standard of care chemotherapy – After consenting to the study, the patients should receive four 28 day cycles of standard of care chemotherapy (FOLFIRINOX). Patients may choose to receive this standard chemotherapy through a local oncologist, and follow-up visits, blood work, and restaging scans during this portion of the study will be scheduled at the discretion of the patient's local oncologist.
3) Pre-immune (After SOC chemo) – Approximately two weeks (+2 to +4 weeks) after the last dose of standard of care chemotherapy, patients at select sites should receive a simulation scan, EUS Fiducial Placement, and EUS Core Biopsy. The EUS core biopsy should occur prior to the administration of radioimmunotherapy.
4) Radioimmunotherapy – Beginning two to four weeks after the last dose of chemotherapy, the patient will receive two 21 day cycles of Cy/GVAX/nivolumab (see dosing delays, section 8.3, if patients are unable to begin radioimmunotherapy due to resolving adverse events related to chemotherapy or any other reason). The second cycle will be combined with SBRT. For logistical reasons, for patients planning to receive 5 days of SBRT, it is recommended that C1D1 of immunotherapy commence on a Monday (so that SBRT can proceed over a continuous Monday through Friday period).
5) Surgical evaluation – Approximately two weeks after the last dose of SBRT the patient will be restaged and assessed for surgical resectability. For patients who are determined to be surgically resectable, surgical resection will be scheduled at the discretion of the treating surgeon but will generally occur within 30 days of surgical evaluation.
6) Off study treatment – A mandatory Off Study/Safety Follow-Up Visit should be performed 30-60 days after surgical resection has been performed (or 30 days +/- 7 days after the last infusion of study medication in patients who are determined not to be surgical candidates, or within 7 days prior to initiation of a new anti-cancer treatment, whichever comes first). After the off-study treatment visit, subjects will be contacted every 12 weeks (+/- 2 weeks) to monitor OS until death, withdrawal of consent, or study closure.

12.1 Study Calendar

	Consent (pre-SOC chemo)	Pre-immune (After SOC chemo)	Immune C1		Immune C2		Surgical Eval	Off-Study Treatment[14]
			D1	D2	D1	D2		
Visit Window (days)[1]	-28 to 28[17]		-	-	+/- 3	-	+/-7	-
Intervention								
Cyclophosphamide			X		X			
GVAX				X		X		
Nivolumab			X		X			
SBRT x 5 or 6 days					X->			
CLINICAL ASSESSMENTS/TESTS								
Informed consent	X							
Inclusion/exclusion criteria	X							
Demographics	X							
Medical History[2]	X							
Concurrent medications	X	X			X		X	X
Vital Signs and pulse ox[3]	X	X		X	X	X	X	X
Physical exam[4]	X	X			X		X	X
Performance status	X	X			X		X	X
Height	X							
Weight	X	X			X		X	X
CBC with differential[5]	X	X[6]			X		X	X
CMP[5,7]	X	X[6]			X		X	X
TSH[5,8]		X[6]			X		X	X
Serum/Urine Preg[9]	X	X[6]			X			
Adverse event evaluation		X[10]			X		X	
Vaccine Site Assessment					X		X	X
Simulation Scan		X						
EUS Fiducial Placement		X						
Surgical Evaluation	X						X	
ASSESSMENT OF RESPONSE AND CORRELATIVE STUDIES								
EUS Core Biopsy/ Surgical Specimen[16, 18]		X					X	
Archival tumor sample	X							
Radiographic evaluation[11]	X	X[12]					X	
CA 19-9	X	X			X		X	X
Whole blood for plasma (up to 40cc)[18]	X[15]	X[13]					X	X
Whole blood for PBL (up to 120cc)[18]		X[13]					X	X
Serum (up to 10cc)[18]		X[13]					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. Telemedicine acknowledgement will be obtained in accordance with the Guidance for Use of Telemedicine in Research. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions.

1) Longer delays to be approved by the sponsor
2) 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, and date of initial diagnosis.
3) Blood pressure, pulse, respiratory rate, and temperature are required as indicated. Pulse oximetry will be obtained at baseline if available and prior to each cycle of therapy only. Vitals should be collected after CY administration, prior to and after nivolumab administration, and prior

to and after GVAX pancreas vaccine administration. Presence of fever alone does not indicate subject is not clinically stable.

4) 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.
5) Labs may be collected within a window of up to 4 days prior to dosing. Unexpected Grade 3 or greater laboratory abnormalities should be repeated within 24-72 hours if clinically indicated and monitored as necessary to determine if event meets toxicity criteria.
6) Pre-immune screening bloodwork does not need to be repeated if performed within 4 days of C1D1. TSH and CA 19-9 only need to be completed at either Pre-Immune Visit or at C1D1. If completed at Pre-Immune time point then TSH and CA 19-9 do not need to be repeated even if greater than 4 days prior to dosing.
7) Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
8) T3 and Free T4 to be checked reflexively if TSH is abnormal
9) Serum or urine pregnancy for women of childbearing potential should be completed within 24 hours of first dose of Cy/Nivolumab and then monthly thereafter.
10) Prior to the administration of immunotherapy to assess baseline toxicity due to chemotherapy.
11) Radiographic evaluations and tumor measurements will be performed with contrast CT chest/abdomen/pelvis. Noncontrast CT chest/abdomen/pelvis or nonconstrast CT Chest and MRI Abdomen/pelvis will be performed in subjects with contrast allergies.
12) Repeat imaging is only necessary in patients who have not received at least one restaging CT, MRI, or PET/CT after completion of the first two 28 day cycles of chemotherapy as part of standard of care therapy, to exclude progressive and/or metastatic disease.
13) Prior to the administration of immunotherapy. If completed at Pre-Immune Visit research labs do not need to be collected again at Immune C1.
14) Subjects will be contacted (by phone or email) every three months (+/- 2 weeks) to monitor OS until until death, withdrawal of consent, or study closure, whichever occurs first. Information of other cancer therapies after discontinuation from the study treatment will also be collected. In addition, SAEs that occur within 100 days (+14 day reporting window) of the end of treatment or before initiation of a new antineoplastic treatment should also be followed and recorded.
15) Research blood draw at consent visit is optional and has a visit window of +2 weeks from time of consent
16) Biopsy will occur at select sites. Surgical specimen or intraoperative biopsy (if surgery is attempted but aborted) will also be obtained at the time of surgical resection.
17) Study consent can be obtained up until 28 days following the first administration of chemotherapy but cannot occur beyond one cycle (1 month or 28 days)
18) Research samples will be collected at the discretion of the PI based on availability of supplies and safety of patient and staff.

13. MEASUREMENT OF EFFECT

13.1 Definitions

13.1.1 Evaluable

Evaluable for toxicity. All enrolled subjects are evaluable for toxicity. Monitoring of unacceptable toxicity will focus on patients receiving any part of one dose of immunotherapy (any component of Cy/GVAX/nivolumab) in order to exclude expected toxicities related to chemotherapy or resection.

Evaluable for response. All subjects who have received at least one dose of treatment for pancreatic cancer (including chemotherapy) as part of this study and undergo a surgical evaluation are evaluable for response. Methods for evaluation of response are described below.

Evaluable for CD8 cell density (primary outcome). All subjects who have received at least one dose of investigational agent, undergo surgery or intraoperative biopsy, and have sufficient biopsy for CD8 cell density evaluation.

Note: Patients enrolled with bilirubin >1.5 x ULN who are not able to be treated with experimental therapy due to elevated bilirubin will be considered not evaluable and will be replaced.

13.1.2 CD8 cell density

CD8 cell density is defined as the number of CD8+ cells per area assessed (e.g. # cells/mm^2).

13.1.3 R0 resection rate

R0 resection is defined by a microscopically margin-negative resection, in which no tumor (gross or microscopic) remains in the primary tumor bed.

13.1.4 Resection rate

Proportion of patients who go on to receive a surgical resection.

13.1.5 pCR rate in surgical specimens

The pCR rate is defined as the proportion of patients who receive a definitive surgical resection with no residual cancer in the primary pancreatic tissue or nodes (ypT0ypN0).

13.1.6 Distant metastases free survival (DMFS)

DMFS is defined as the duration of time from start of enrollment in study to identification of recurrent disease on imaging or death, whichever occurs first. The pattern of recurrence (local vs. metastatic, or both) will also be inquired. Individuals will be censored at the date

of the last scan if no event occurs.

13.1.7 Overall Survival (OS)

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

13.1.8 Overall Response Rate (ORR)

ORR is defined as the proportion of patients achieving a complete response (CR) or partial response (PR) based on the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) **(See Appendix D**).

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 time of study enrollment. 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 (during and 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 the time of study enrollment 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 study enrollment and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

13.1.9 ptDNA

ptDNA will be assessed as the presence or absence of detectable neoepitopes for the

common Kras mutations in peripheral blood.

14. DATA REPORTING AND STUDY MONITORING

14.1 Data Collection and Processing

All information will be collected on study-specific CRFs by study staff. These data will be reviewed for completeness and accuracy by the Principal Investigator at each site.

CRFs will be used to capture study results and data. The study coordinator or other authorized study personnel will transcribe data from source documents onto eCRFs. Before or between visits, the Protocol Chair, IND Sponsor, or designee may request copies of the CRFs for preliminary medical review. Once the CRFs are complete and source-verified, the investigator must sign and date all required pages, verifying the accuracy of all data contained within the CRF. Training will be provided on proper completion of CRFs.

Protocol Chair

The Protocol Chair and/or designee is responsible for performing the following tasks:

- Coordinating, developing, submitting, and obtaining approval for the protocol as well as its subsequent amendments.
- Assuring that all participating institutions are using the correct version of the protocol.
- Taking responsibility for the overall conduct of the study at all participating institutions and for monitoring the progress of the study.
- Reviewing and ensuring reporting of SAE
- Reviewing data from all sites.

Coordinating Center

The Coordinating Center (or its representative) is responsible for performing the following tasks:

- Ensuring that IRB approval has been obtained at each participating site prior to the first subject registration at that site, and maintaining copies of IRB approvals from each site.
- Monitoring subject registration.
- Collecting and compiling data from each site.
- Establishing procedures for documentation, reporting, and submitting of AE's and SAE's to the Protocol Chair, and all applicable parties.
- Facilitating audits by securing selected source documents and research records from participating sites for audit, or by auditing at participating sites.

Participating Sites

Participating sites are responsible for performing the following tasks:

- Following the protocol as written, and the guidelines of Good Clinical Practice (GCP).
- Submitting data to the Coordinating Center.
- Consent subjects promptly and randomize eligible subjects in EDC.
- Providing sufficient experienced clinical and administrative staff and adequate facilities and equipment to conduct a collaborative trial according to the protocol.

- Maintaining regulatory binders on site and providing copies of all required documents to the Coordinating Center.
- Collecting and submitting data according to the schedule specified by the protocol.

14.2 Study Documentation

14.2.1 Case Report Forms and Source Documentation

The investigator must make study data accessible to the site monitor, to other authorized representatives of the IND Sponsor (or designee) and to the appropriate regulatory authority inspectors. The original CRF for each subject will be checked against source documents at the study site by the site monitor.

14.2.2 Retention of Study Documents

According to ICH E6, Section 4.9, all CRFs, as well as supporting paper and electronic documentation and administrative records, must be retained for at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications, or at least 2 years have elapsed since the formal discontinuation of clinical development of an individual product. Longer retention periods may apply. The IND Sponsor will notify investigators as to when documents no longer need to be retained. No study documents will be destroyed or moved to a new location without prior written approval from the IND Sponsor. If the investigator relocates, retires or withdraws from the clinical study for any reason, all records required to be maintained for the study should be transferred to an agreed-upon designee, such as another investigator at the institution where the study was conducted.

Audit trails for electronic documents must be retained for a period at least as long as that required for the subject electronic records to which they pertain. The investigator must retain either the original or a certified copy of audit trails.

14.2.3 Data Confidentiality and Subject Anonymity

All information about the nature of the proposed investigation provided by the IND Sponsor or their representative to the investigator (with the exception of information required by law or regulations to be disclosed to the IRB, the subject or the appropriate regulatory authority) must be kept in confidence by the investigator.

The anonymity of participating subjects must be maintained. Subjects will be identified by their initials and an assigned subject number on CRFs and other documents retrieved from the site or sent to the IND Sponsor, study monitor, BMS, regulatory agencies, or central laboratories/reviewers. Documents that identify the subject (e.g., the signed ICF) must be maintained in strict confidence by the investigator, except to the extent necessary to allow auditing by the appropriate regulatory authority, the study monitor, IND Sponsor or their representative.

14.3 Protocol Compliance

Substantive changes in the protocol include changes that affect the safety of subjects or changes that alter the scope of the investigation, the scientific quality of the study, the experimental design, dosages, assessment variable(s), the number of subjects treated or the subject selection criteria. A protocol amendment must receive IRB approval before implementation. In parallel with the IRB approval process, the protocol amendment will be submitted to the appropriate regulatory authority as an amendment to the regulatory submission under which the study is being conducted. If a protocol amendment requires changes in the ICF, the revised ICF prepared by the investigator must also be approved by the IND Sponsor, the study monitor and the IRB before implementation.

Emergency departures from the protocol that eliminate an apparent immediate hazard to a particular subject and that are deemed crucial for the safety and well-being of that subject may be instituted for that subject only. The investigator or the attending physician also will contact the Protocol Chair and/or designee as soon as possible in the case of such a departure. These departures do not require preapproval by the IRB; however, the IRB and the Protocol Chair and/ or designee must be notified in writing as soon as possible after the departure has been made. In addition, the investigator will document in the subject's CRF the reasons for the protocol deviation and the ensuing events.

14.4 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. Eligibility for all sites will be monitored by the Protocol Chair. The protocol will be internally monitored by the Principal Investigator at each site. 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. (per the DSMP). External monitoring will occur according to the following guidelines:

Johns Hopkins SKCCC: The protocol will be monitored externally by the SKCCC CRO in accordance with SKCCC guidelines. Trial monitoring and reporting will be done through the Safety Monitoring Committee (SMC) at SKCCC.

Participating site(s): The protocol will be monitored by authorized representatives of the coordinating center. A report of the reviews will be submitted to the Johns Hopkins principal investigator and SKCCC CRO.

Authorized representatives of the Coordinating Center may visit the satellite sites to perform audits or inspections, including source data verification. The purpose of these audits or inspections is to systematically and independently examine all trial-related activities and documents to determine whether these activities were conducted and data

were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), and any applicable regulatory requirements.

Additional data and safety monitoring oversight will also be performed by the SKCCC Safety Monitoring Committee (SMC - as defined in the DSMP) and a Medical Expert Committee (MEC) as detailed below. The purpose of these audits or inspections is to systematically and independently examine all trial-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), and any applicable regulatory requirements. The Medical Expert Committee (MEC) for this clinical study contains three oncologists from other disciplines who are not affiliated with this clinical trial protocol. The MEC will review safety data on at least a semi-annual basis. The MEC will provide a written summary of each assessment to the IND Sponsor after each meeting. In turn, the study team will forward these summaries to the JHU SKCCC SMC. The operating plan of the MEC will be as follows:

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

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

15. STATISTICAL CONSIDERATIONS

15.1 Overview

The proposed study is an open-label, single-arm phase II study of neoadjuvant sequential chemotherapy, SBRT, and Cy/GVAX/nivolumab immunotherapy in patient with borderline resectable pancreatic ductal adenocarcinoma (BR-PDAC). The primary objective of the trial is to determine whether sequential chemotherapy, SBRT, and Cy/GVAX/nivolumab administered in this patient population increases CD8 cell count in resected tumor tissue compared to historical controls. The study is planned with up to 32 participants. The study will be continuously monitored for adverse events.

15.2 Sample Size and Accrual

A total of 20 historical control samples are available from BR-PDAC patients treated with

FOLFIRINOX and SBRT prior to resection. We expect that approximately 15 out of the 32 (47%) participants enrolled in this study will be evaluable for CD8 cell density, i.e. received at least one dose of treatment for pancreatic cancer (including chemotherapy) as part of this study, undergo surgery, and have sufficient biopsy for CD8 cell density evaluation. A sample size of 15 evaluable patients and 20 controls would provide 80% power to detect a CD8 count that is 3.01-fold higher for the novel treatment samples as compared to the control treatment samples.

More than 100 patients with BR-PDAC annually present for evaluation and treatment at JHH, MGH, and MCW. We anticipate the majority of these patients would be potentially eligible for enrollment on this the proposed study.

15.3 Analysis

The primary outcome is the CD8 count, which will be measured on the log-scale due to skewness. Summary statistics (e.g. median, range, mean, standard deviation) and plots (e.g. boxplots, histograms) will be used to explore the data. Log-linear models will be used to compare the CD8 count between samples from patients in the study and the historical control as well as to explore characteristics associated with CD8 count.

An important secondary outcome is the proportion of patients with a pathologic CR at week 21 (the time of surgical resection). The proportion with exact 95% confidences intervals will be computed. Individuals who are lost to follow-up prior to surgical evaluation, or who do not undergo surgical resection, will be counted as not achieving a pathologic CR. Other binary outcomes (e.g. resection rate) will be analyzed in a similar manner.

Time to event outcomes (e.g. OS, DMSF, time to pathologic CR) will be summarized using Kaplan-Meier estimates of the survival function. The median and proportion alive at specific time points (e.g. 6 months, 1 year) will be calculated with 95% confidence intervals.

Tumor biopsies will be collected at during EUS and fiducial placement at select sites. A second sample will be collected at approximately week 25 either during resection or, for those whose surgery is attempted but aborted, with an intraoperative biopsy. In prior studies, we have been able to obtain paired tumor samples in ~ 65% of patients (N = 32). The remaining 35% were missing due to patient refusal, loss to follow-up, or issues with the sample quality. Summary statistics (e.g. mean, standard deviation, median, IQR, proportion, correlation) will be calculated at both time-points and graphical techniques (e.g. boxplots, histograms) will be used to visual inspect the data. Log or other transformations will be applied as need based upon the exploratory analysis. Cross-sectional comparisons between different immunologic endpoints (e.g. correlation, Fisher's exact test, t-tests, scatter plots) will be explored. Paired t-tests, or Wilcoxon rank sum tests if appropriate, will be used to evaluate changes in paired continuous measurements. The percent agreement and McNemar's test will be used to compare patterns in paired binary outcomes.

PBL, sera and plasma will be collected throughout and at the end of immunotherapy

treatment. In addition to the cross-section explorations described above spaghetti plots and boxplots over time will be used to graphically visualize longitudinal patterns. Generalized estimating equations will be used to model immunologic outcomes over time while accounting for the correlation between repeated measurements on the same person. Multiple mean (e.g. indicator for each time point, linear function) and correlation (e.g. unstructured, exchangeable, AR(1)) structures will be explored.

Logistic regression and Cox proportional hazards models will be used to assess the relationship between immunologic measurements from tumor, PBL, sera, and plasma samples and clinical outcomes including pathologic CR and OS and DMSF, respectively.

The relationship between tumor tissue with ptDNA will be explored. The percent agreement will be calculated with exact 95% confidence intervals and Fisher's exact test and McNemar's test will be used assess the association between the measurements and imbalances in discordant measurements, respectively. The relationship between presence of detectible ptDNA and binary outcomes (e.g. pCR) will be assessed using standard ROC techniques including ROC curves, sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV). Heagerty's time varying ROC analysis will be used to calculate these metrics for time to event outcomes (e.g. OS, DMSF)[38].

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

Genomic sequencing data will be stored and computations conducted using a JH IT managed subscription of Azure.

15.4 Safety Monitoring

The safety analysis will be performed in all enrolled patients. AE data will be listed individually and will be tabulated by type, grade, and relatedness both overall and by organ class. In addition to raw counts, the rates of AEs will be calculated based (number of events/length of follow-up).

Monitoring of unacceptable toxicities will focus on patients receiving immunotherapy (any component of Cy/GVAX/nivolumab) excluding expected toxicities due to chemotherapy or resection. The proportion of subjects with an unacceptable toxicity (See **Section 7.7**) resulting from immunotherapy will be using a Bayesian stopping guideline. A toxicity level 45% would be considered the upper boundary. We expect the actual toxicity level to be 25%. A Beta (2.5, 5.5) prior, representing a toxicity rate of 31% (slightly above our expected rate), will be used to be conservative. After the first 6 patients have been treated, safety will be monitored continuously. If the probability that the proportion of

unacceptable toxicities exceeds 45% is above 50%, we will halt accrual and re-evaluate the trial. **Table 5** shows the number of toxicities that would need to be observed in order to trigger the stopping guidelines throughout the course of the trial.

Table 5. The number of toxicities needed to trigger stopping guidelines throughout the course of the study.

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

The probability of trigger the stopping guidelines was assessed for a range of true underlying toxicity rates using simulations with 10,000 replicates (**Table 6**). The probability of stopping to re-evaluate is 6.6% if the true proportion with an unacceptable toxicity was 25%. In contrast, the probability of early stopping is 67.0% if the true proportion with an unacceptable toxicity was 45%, the threshold for acceptable levels of toxicity.

Table 6. Probability of triggering a re-evaluation for a range of unacceptable toxicity levels.

True probability of unacceptable toxicity	Number of toxicities needed to trigger re-evaluation
5%	< 0.1%
10%	0.1%
15%	0.9%
20%	2.3%
25%	6.6%
30%	14.2%
35%	27.8%
40%	46.1%
45%	67.0%
50%	84.3%
55%	94.3%

15.5 Interim Analysis for Efficacy

Given the small sample size, no interim efficacy analyses will be performed.

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APPENDIX A: PERFORMANCE STATUS CRITERIA

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

APPENDIX B: MANAGEMENT ALGORITHMS

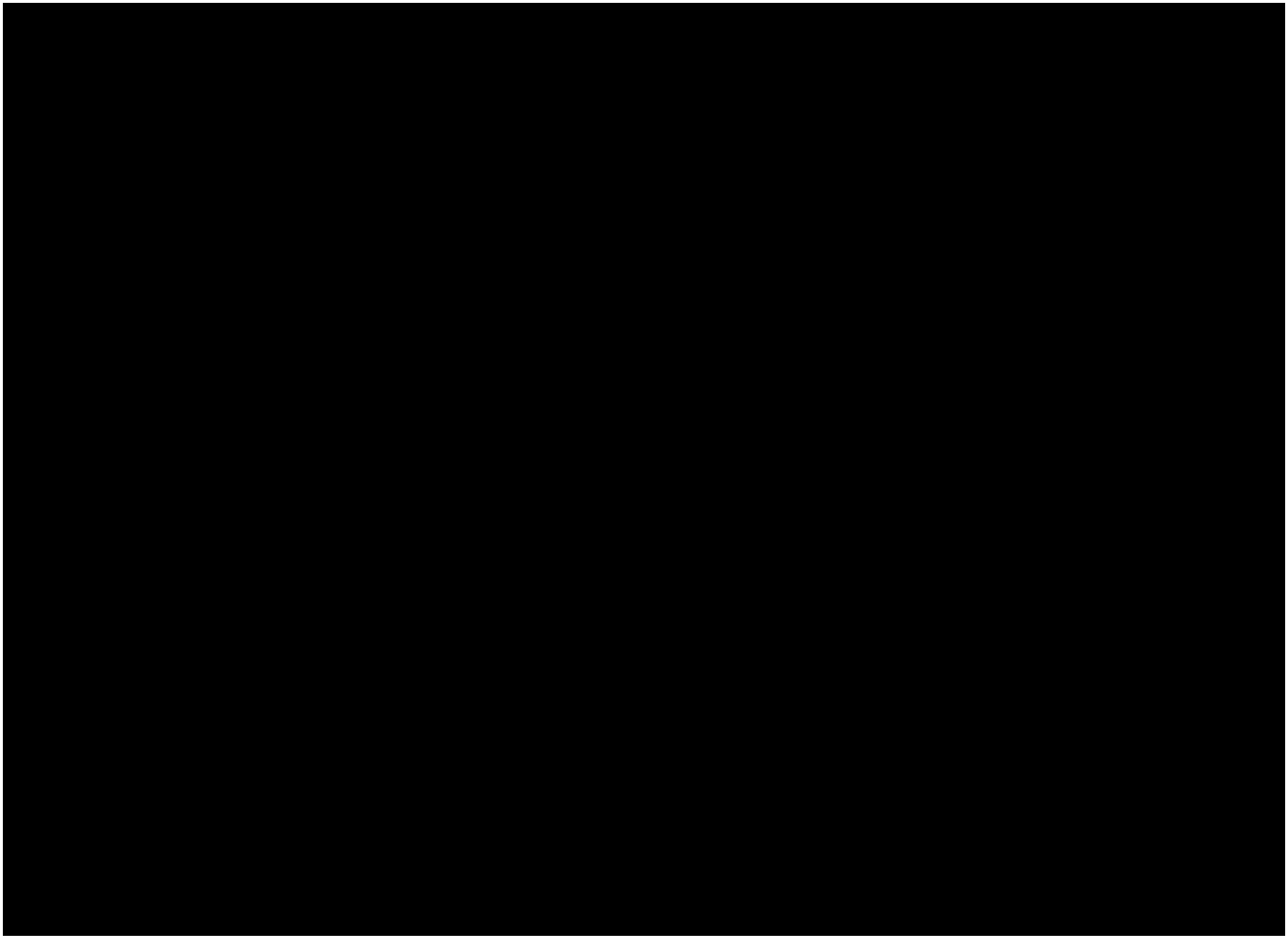
These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the IND Sponsor. The guidance applies to all immuno-oncology (I-O) agents and regimens.

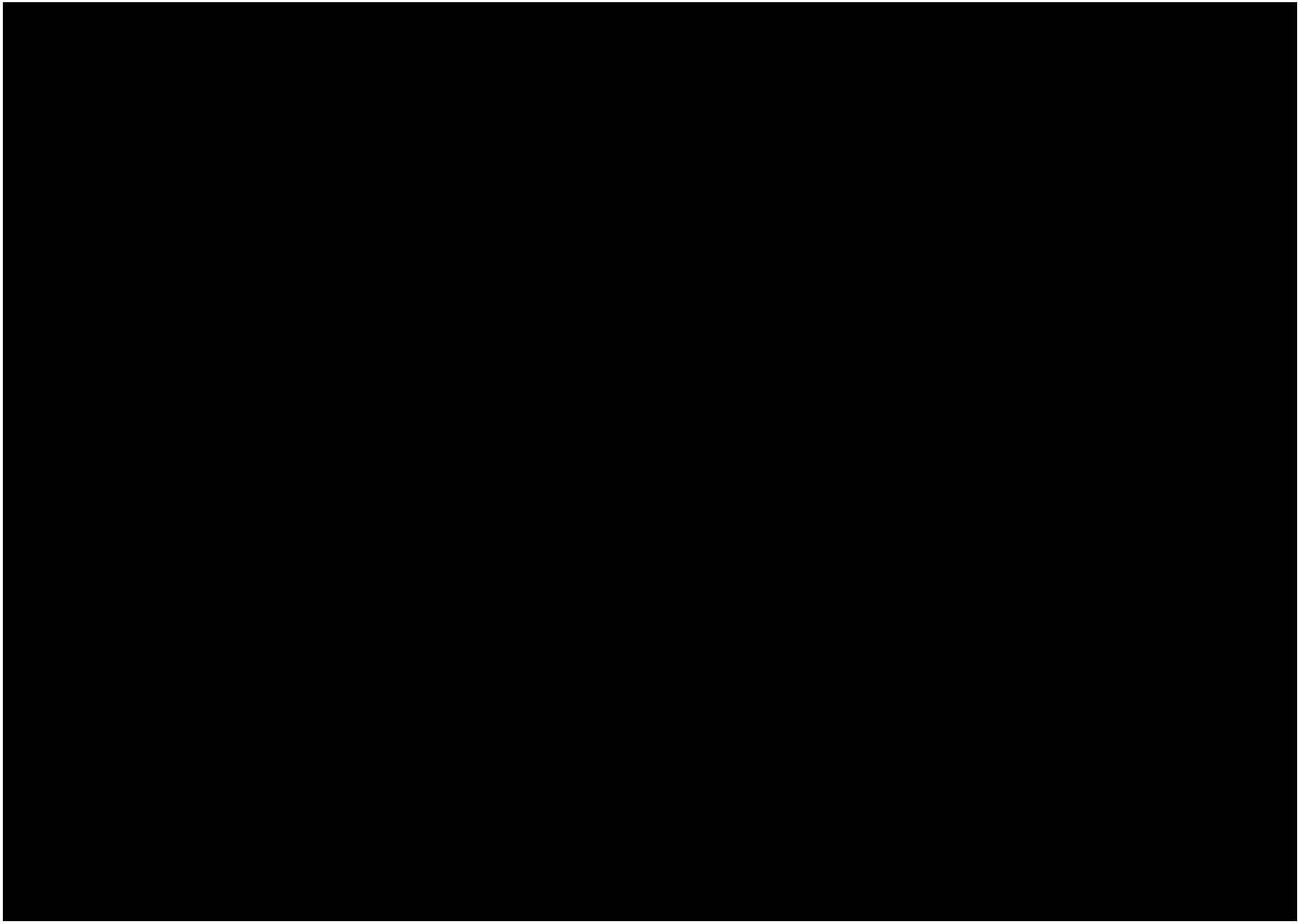
A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

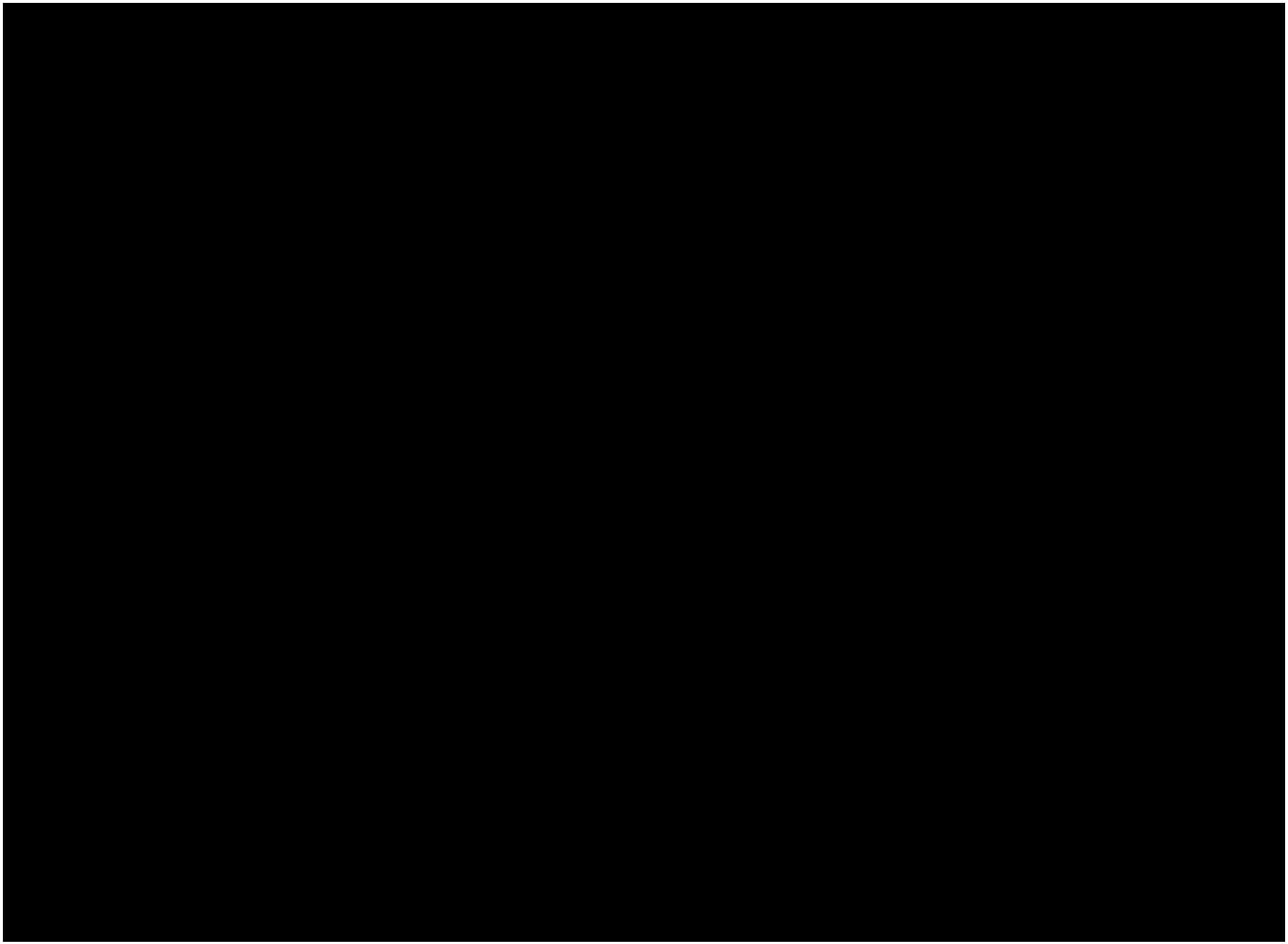
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory subjects with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

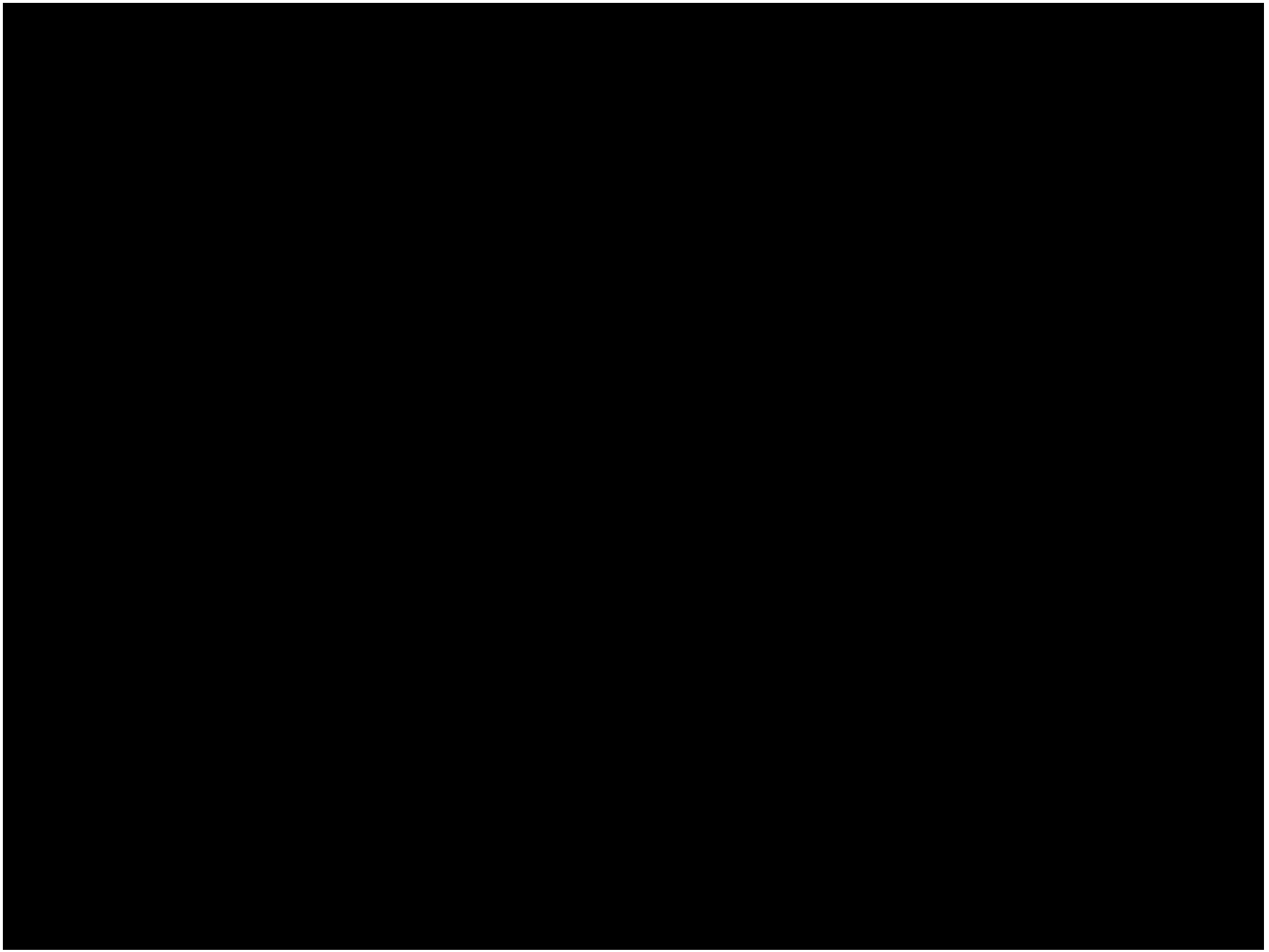
Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

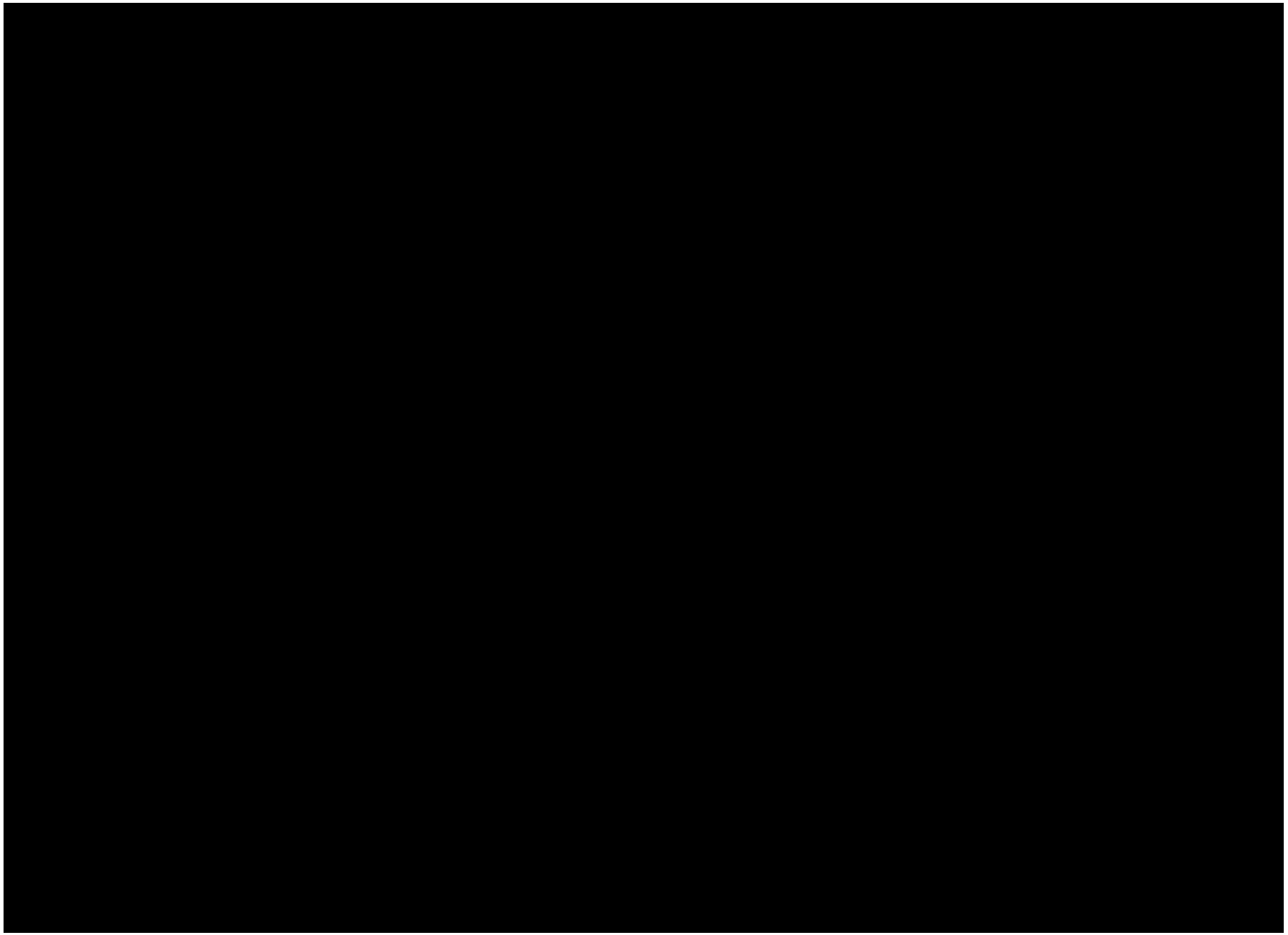
The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

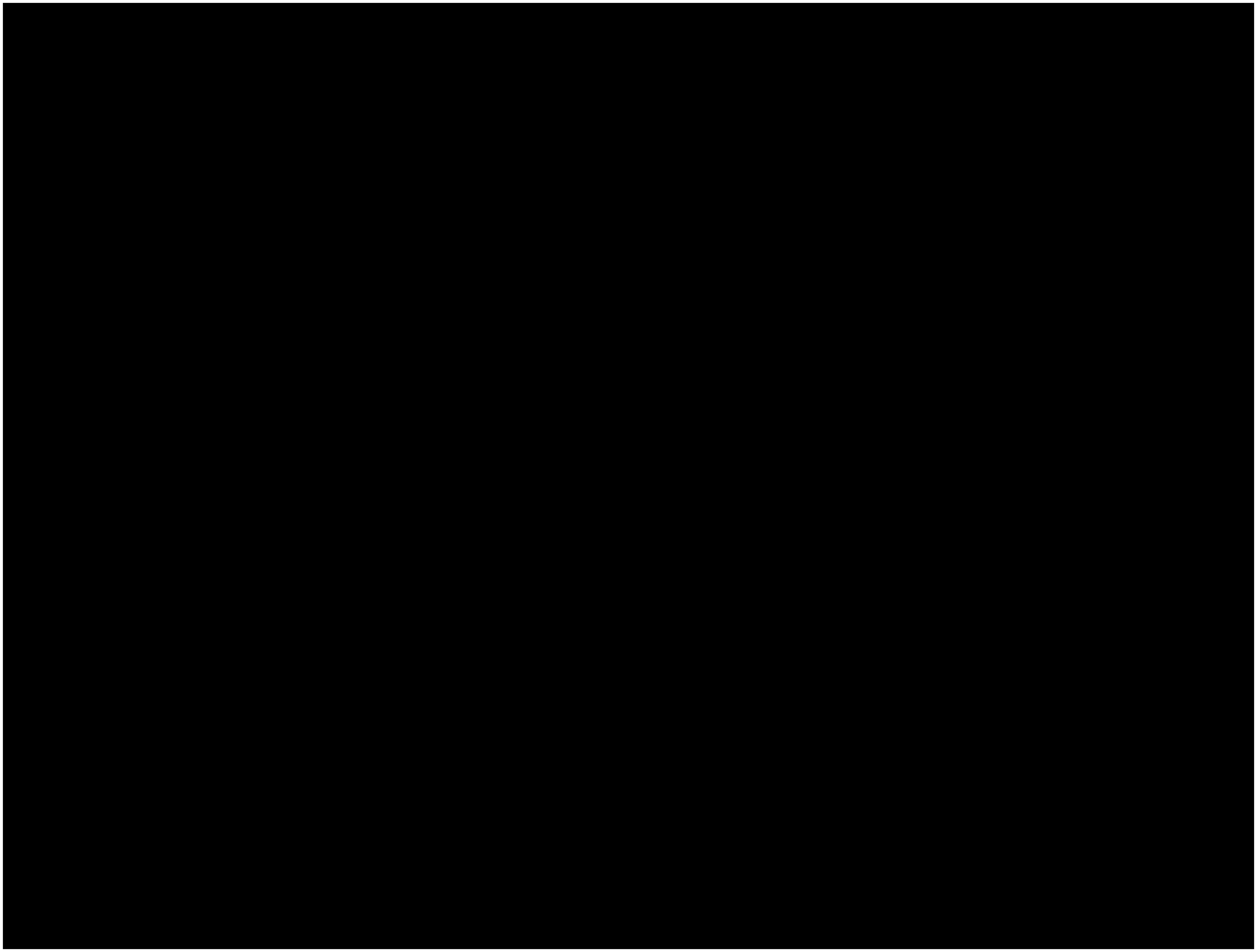












APPENDIX C: SAE REPORTING FORM

Serious Adverse Event Reporting Form

Please notify: Dr. Jaffee within 24 hours [redacted]
BMS within 24 hours [redacted]

Protocol Title:	**A Phase II Clinical Trial of GVAX Pancreas Vaccine (with Cyclophosphamide) in Combination with Nivolumab and Stereotactic Body Radiation Therapy (SBRT) Followed by Definitive Resection for Patients with Borderline Resectable Pancreatic Adenocarcinoma**		
Protocol Number (CA 209-9CY): J1756	**Signature of PI:**	**Principal Investigator:**	**Date:**
Report Type: ☐ **Initial** ☐ **Follow-up** ☐ **Final Follow-up** ☐ **Death** ☐ **Addendum to:**	**Serious Criteria (check all that apply):** ☐ Death ☐ Life-threatening ☐ Hospitalization or Elongation of Existing Hospitalization ☐ Persistent or Significant Disability ☐ Congenital Anomoly ☐ Other Important Medical Event ☐ Cancer ☐ Overdose	**Hospital Admission Date:** **Hospital Discharge Date:**	**Date Event Discovered:**

Section A: Subject Information

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

Section B: Event Information

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

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

Relationship to:	GVAX	CY	Nivolumab	SBRT	Underlying Disease
Unrelated	☐	☐	☐	☐	☐
Related	☐	☐	☐	☐	☐

Section C: Brief Description of the Event:

Section D: Relevant Medical History

Section E: Concomitant Drug (Not related to SAE)

Name of the Drug	Start Date	Stop Date	Route	Dose	Frequency

Section F: Comments

Additional Documents: ☐ Please specify

APPENDIX D: RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) 1.1 CRITERIA FOR EVALUATING RESPONSE IN SOLID TUMORS

RECIST version 1.1 will be used in this study for assessment of tumor response. While either CT or MRI may be used utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

Disease Parameters

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

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable unless there is evidence of progression in the irradiated site. Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

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

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be

recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

Evaluation of Target Lesions

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

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

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

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

Evaluation of Non-Target Lesions

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

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

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

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

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

Evaluation of Best Overall Response

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

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

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

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

Reference

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Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.