TITLE: A Randomized Phase 2 Study of the Safety, Efficacy, and Immune Response of GVAX Pancreas Vaccine (with Cyclophosphamide) and CRS-207 with or without Nivolumab in Patients with Previously Treated Metastatic Pancreatic Adenocarcinoma

Johns Hopkins Protocol #: J14113, IRB00043936

Aduro Biotech, Inc. Protocol #: ADU-CL-06

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***Principal Investigator:** Dr. Dung Le (Protocol Chair)
Sidney Kimmel Comprehensive Cancer Center,
Johns Hopkins University
1650 Orleans Street, Room 407
Baltimore MD 21287
[redacted]

IND Sponsor: Dr. Elizabeth Jaffee
Sidney Kimmel Comprehensive Cancer Center,
Johns Hopkins University
1650 Orleans Street, Room 4M07
Baltimore MD 21287
[redacted]

Contract Research Organization (CRO) Contacts: Diane Felix, Ph.D.
Clinical Trial Manager
Medpace
5375 Medpace Way
Cincinnati, Ohio 45227
[redacted]

Lyon L. Gleich, M.D.
Medical Monitor
Vice President, Medical Affairs
Medpace
5375 Medpace Way
Cincinnati, Ohio 45227
[redacted]

IND:	BB IND 16147
Bristol-Myers Squibb Supplied Agent:	Nivolumab (BMS-936558; anti-PD-1 mAb)
Aduro Biotech, Inc. Supplied Agent:	CRS-207 (*Lm* Δ*actA*/Δ*inlB*/hMesothelin)
Johns Hopkins University Supplied Agent:	GVAX pancreas vaccine (Panc 10.05 pcDNA-1/GM-Neo, Panc 6.03 pcDNA-1/GM-Neo)
Commercial Agent:	Cyclophosphamide (CY, Cytoxan®)
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1. OBJECTIVES

1.1 Primary Objectives

The primary objective of this study is to compare the overall survival (OS) of subjects with previously treated metastatic pancreatic cancer treated with cyclophosphamide (CY)/nivolumab/GVAX pancreas vaccine followed by nivolumab/CRS-207 (Arm A) to subjects treated with CY/GVAX pancreas vaccine followed by CRS-207 (Arm B).

1.2 Secondary Objectives

1.2.1 To assess safety and characterize toxicities of heterologous prime boost vaccination with anti-programmed death-1 (PD-1) blockade in subjects with metastatic pancreatic adenocarcinoma and compare between treatment arms.

1.2.2 To assess progression-free survival (PFS), immune-related progression-free survival (irPFS), and time to progression (TTP) and compare between treatment arms.

1.2.3 To assess the objective response rate by Response Evaluation Criteria for Solid Tumors (RECIST) 1.1 and compare between treatment arms.

1.2.4 To measure tumor marker kinetics (CA 19-9) in subjects receiving treatment and correlate with OS, PFS and best overall response and compare between treatment arms.

1.3 Exploratory Objectives

1.3.1 To assess the objective response rate and duration of response by immune-related response criteria (irRC) and compare between treatment arms.

1.3.2 To collect peripheral blood mononuclear cells (PBMC), plasma, and serum to identify potential therapeutic targets and biomarkers and predictors of response (OS, PFS and best overall response) and autoimmune toxicity.

- Measure pre- and post-treatment changes in PBMCs including effector, helper, and regulatory T cells, NK cells, monocytes, and macrophages through subset analysis and gene expression profiling.

- Correlate induction of *Listeria monocytogenes* (*Lm*)- and mesothelin antigen-specific T cell responses and changes to the T cell epitope repertoire with OS, PFS and best overall response.

- Correlate telomere length of lymphocytes to help predict response (OS, PFS and best overall response).

- Correlate the induction of thyroglobulin and galectin-3 antibody responses with response (OS, PFS and best overall response).

- Proteomic approaches will be used on pre- and post-treatment sera to identify targets and biomarkers of response (OS, PFS and best overall response) or toxicity.

1.3.3 To collect archived tissue and pre- and post-treatment biopsies to test for predictors of response (OS, PFS and best overall response) and future targets for combinatorial therapy.

- Immunohistochemistry (IHC) and/or gene expression profiling will be used to compare the nature of tumors and immune infiltrates for responders versus non-responders.
- Up-regulation of immune inhibitory molecules (such as programmed death-ligand 1 [PD-L1]) will be evaluated in the pre- and post-treatment samples.
- Proteomic approaches to quantify protein expression and activation of specific signaling pathways in tumors from responders versus non-responders

1.3.4 To collect stool samples pre- and post-treatment to identify candidate gut microbial biomarkers and predictors of response (OS, PFS and best overall response)

- Microbial community analysis via 16S V4 sequencing to correlate gut microbiome composition with response (OS, PFS and best overall response)
- Whole metagenome functional profiling analysis via shotgun sequencing to correlate microbiome composition and microbial functions and pathways with response (OS, PFS and best overall response)

1.4 Study Design

This is a multi-center, open-label, randomized, phase 2 study to evaluate the safety and clinical activity of CY/nivolumab/GVAX pancreas vaccine followed by nivolumab/CRS-207 in subjects with metastatic pancreatic adenocarcinoma who received and failed only 1 prior chemotherapy regimen for metastatic disease. The primary endpoint of the trial is OS. The OS of subjects treated with CY/ nivolumab/GVAX pancreas vaccine followed by nivolumab/CRS-207 (Arm A) will be compared to subjects treated with CY/GVAX pancreas vaccine followed by CRS-207 (Arm B). Approximately 108 subjects with previously treated metastatic pancreatic cancer will be enrolled and randomized 1:1 to the two treatment arms to achieve 102 treated subjects.

The study will consist of a screening period (within 21 days of first dose, inclusive of a randomization period of up to 7 days of first dose), a treatment period per the table below, and a follow-up period.

TREATMENT SCHEDULE				
Arm	**CY**	**Nivolumab**	**GVAX**	**CRS-207**
A	Day 1, Cycles 1, 2	Day 1, Cycles 1, 2, 3, 4, 5, 6	Day 2, Cycles 1, 2	Day 2, Cycles 3, 4, 5, 6
B	Day 1, Cycles 1, 2	None	Day 2, Cycles 1, 2	Day 1, Cycles 3, 4, 5, 6

Subjects on both arms will receive treatment every 3 weeks for 6 cycles of treatment within a course. A course of treatment will be 20 weeks, with 16 weeks of treatment followed by an end-of-course (EOC) evaluation approximately 4 weeks after the last study treatment administration in the course. Treatment Arm A will include 2 cycles of CY/nivolumab/GVAX pancreas vaccine, followed by 4 cycles of nivolumab/CRS-207. Treatment Arm B will include 2 cycles of CY/GVAX pancreas vaccine followed by 4 cycles of CRS-207. Subjects will come to the clinic for dosing and/or assessments on Days 1 and 2 of each cycle and additional days for safety and immune monitoring follow-up per the study schedules in **Section 10**.

No dose escalations or reductions are allowed. Enrollment will continue until 102 subjects have received at least one dose of study treatment. It is estimated that 5% of the subjects will not receive treatment so approximately 108 randomized subjects are expected to achieve 102 treated subjects. Subjects who are required to stop treatment with nivolumab due to toxicity may stay on study treatment and receive CY/GVAX pancreas vaccine followed by CRS-207.

The proportion of treated subjects with unacceptable toxicity will be monitored using a Bayesian stopping guideline (**Section 5.8**). Subjects will be randomized until 6 subjects have been treated in Arm A (approximately 12 subjects in Arms A and B) and followed for at least 8 weeks (so that 6 Arm A subjects have received 2 cycles of CY/nivolumab/GVAX pancreas vaccine and at least one cycle of nivolumab/CRS-207). Accrual will be suspended until the toxicity levels have been determined to be acceptable (i.e. confirmation that less than 3 subjects experience unacceptable toxicities during the first 8 weeks in Arm A). Then, the remaining participants will be enrolled and monitored routinely. For purposes of determining unacceptable toxicity during the initial 8 weeks of treatment, subjects will be followed for treatment-related ≥ grade 4 AEs or grade 3 AEs not improving to ≤ grade 2 under therapy within 2 weeks [redacted]
Asymptomatic amylase, lipase elevation, hypophosphatemia, and lymphopenia will not be considered unacceptable toxicities. In addition, ≥ grade 2 eye pain or reduction of visual acuity that does not respond to topical therapy and does not improve to ≤ grade 1 severity within 2 weeks of starting therapy, or requires systemic therapy is an unacceptable toxicity.

Immune and clinical responses will be evaluated through the following methods at baseline and during treatment: 1. tumor biopsies, 2. PBMCs, 3. serum and plasma, and 4. computed tomography (CT) scans (magnetic resonance imaging [MRI], if CT contraindicated) will be obtained for assessment of activity and correlative studies. Tumor assessments will be made using RECIST 1.1 and irRC.

At the investigator's discretion, subjects may receive additional courses of the assigned treatment

regimen if they are clinically stable and meet dosing eligibility criteria. All subjects may continue in the treatment period until discontinuation due to unacceptable toxicity, lack of clinical benefit as determined by the investigator, or termination of the study by sponsor. Subjects may continue on treatment with radiographic disease progression if subject is clinically stable and investigator believes the treatment is providing benefit. Criteria for removal from treatment are found in **Section 5.11**. Subjects will return to the study site no more than 4 weeks after the final administration of study treatment for an end-of-treatment (EOT) evaluation. [redacted] Subjects who are still receiving treatment at the time of study close may complete the current treatment course and the EOT evaluation prior to transitioning to long-term follow-up. Subjects will be considered in the treatment period until 4 weeks after the last dose of study drug. Blood cultures through a peripheral vein and also through a central line (if applicable) will be collected to monitor for the presence of CRS-207 per **Section 5.14**.

After completion of treatment and EOT assessments, all subjects, including those who did not receive treatment, will continue to be followed every 12 weeks by telephone, e-mail, or optional clinic visit until death, withdrawal of consent, or closure of study. Subjects treated in Arm A will also be contacted at 100 days from the last dose of nivolumab or 28 days from the last dose of cyclophosphamide, GVAX, or CRS-207 if the subject never received nivolumab or is no longer receiving nivolumab due to toxicity, whichever reporting period is longer. The visit window for conducting this final visit is either 100 +14 days or 28 + 7 days. Information on survival and new cancer therapies will be collected.

All subjects who discontinue study treatment should continue to be monitored for disease status by radiologic imaging every 12 weeks until: the 1) start of a new antineoplastic therapy (information of the new cancer therapy will be collected), 2) death, 3) withdrawal of consent, or 4) the close of the study, whichever occurs first.

All subjects will be followed for at least 4 weeks after their last dose of study drug for the development of adverse events (AEs). Serious adverse events (SAEs) that occur within 100 days after the last dose of nivolumab for subjects in Arm A or for 28 days from the last dose of cyclophosphamide, GVAX, or CRS-207, if the subject never received or is no longer receiving nivolumab due to toxicity, whichever reporting period is longer. SAEs will be collected for 28 days after last dose of study drug for subjects in Arm B, or until initiation of a new anti-cancer treatment, whichever occurs first. Subjects who are discontinued from study treatment due to an unacceptable treatment-related AE will be monitored for the resolution of the AE to $\leq$ grade 1 or stabilization or until initiation of a new therapy for their cancer, whichever occurs first.

The study will be closed when all subjects have been followed for at least 12 months and the final analysis timing criteria have been met, or when all subjects have withdrawn from study. The final analysis will be conducted when the first of the following has occurred: 84 deaths in treated subjects, 12 months after the last treated subject was enrolled, or study is closed by sponsor. At the conclusion of the study, all remaining subjects will be offered enrollment in a long-term follow-up study and continue to be followed for survival and clinical and immunological responses.

An independent Data Monitoring Committee (DMC) will monitor accumulating safety data at intervals throughout the study. Additionally, an interim analysis will be conducted to assess efficacy in the context of subject risk/benefit when approximately 50% of the expected deaths in treatment subjects have occurred (approximately 42 deaths).

2. BACKGROUND

2.1 Study Disease

In 2013, there were an estimated 45,220 new cases of pancreatic cancer diagnosed in the United States[1]. Generally, most new cases of pancreatic cancer are advanced with extensive tumor growth usually due to the lack of symptoms during the early stages of the disease. As a result, few patients are considered candidates for surgical resection. Patients with advanced pancreatic cancer are usually treated with chemotherapy in an effort to improve survival and alleviate symptoms. Median survival time ranges from 4 to 6 months in patients with metastatic disease. With treatment, survival has improved to 6 to 11 months[2,3]. Overall, the 5-year survival rate is about 6% for all stages combined and decreases to 2% for patients with metastatic pancreatic cancer[4]. Currently, there are a few standard therapy options for patients. Single-agent gemcitabine was FDA approved based on a comparative study between gemcitabine and 5-FU. Gemcitabine produced significant improvement in disease-related symptoms and prolonged survival (1-year survival: 18% versus 2%, respectively)[5]. Subsequently, the oral tyrosine kinase inhibitor, erlotinib, was approved in combination with gemcitabine based on a slight increase in median survival over gemcitabine alone (6.24 months compared to 5.91 months)[6]. Other phase 3 studies testing combination regimens have been disappointing. More recently, a randomized phase 3 study performed in France comparing FOLFIRINOX (5-FU/leucovorin/irinotecan/oxaliplatin) to gemcitabine as first-line therapy resulted in an improvement in survival of 11.1 months versus 6.8 months[2]. While this regimen is being used, there are still concerns about its potential toxicity in a North American population and it is being reserved for the most fit patients. Nab-paclitaxel has now been approved in combination with gemcitabine as first-line therapy with a median survival of 8.5 months compared to 6.7 months with gemcitabine alone[7]. Therapies for patients with metastatic pancreatic cancer are urgently needed, in particular there are no therapies currently approved for previously treated patients with metastatic disease. Novel approaches, such as immunotherapy, are showing promise in this very difficult cancer.

2.2 Rationale

Immune tolerance mechanisms both at the systemic level and in the tumor microenvironment inhibit activity of immunotherapy in pancreatic ductal adenocarcinoma (PDA). Combinatorial strategies aimed at priming tumor antigen-specific T cells while simultaneously blocking negative immune checkpoints will be necessary to show an effect in PDA. There is increasing interest in the role of immunotherapy in the treatment of cancers. Ipilimumab (Yervoy®), is an antagonist antibody to cytotoxic T-lymphocyte antigen-4 (CTLA-4) which downregulates T cell activation. Ipilimumab has been approved for the treatment of metastatic melanoma and Provenge® (sipuleucel-T), an autologous dendritic cell-based vaccine, has been approved for prostate cancer[8,9]. Another immune checkpoint blocker, PD-1, is showing promising results in melanoma, renal cell, and lung cancer[10,11]. Despite all of the excitement, diseases such as PDA, are unlikely to respond to single-agent therapy. Unlike melanoma, there are very few tumor-

infiltrating lymphocytes at baseline to be targeted by these agents. Vaccines are necessary to prime and expand tumor-specific T cells to infiltrate the tumor and agents designed to turn off the brakes on the T cells can then promote tumor regression.

The optimal approach to elicit anti-tumor immunity would include the use of a vaccine strategy that has shown promising results in patients with pancreatic cancer in combination with an agent that inhibits negative T cell signaling, such as anti-PD-1. One synergistic vaccine strategy is the use of heterologous prime-boost vaccinations integrating two, distinct vaccine vectors to optimize immune responses. In murine models, GVAX (tumor cells modified to express granulocyte macrophage-colony stimulating factor [GM-CSF]) followed by an attenuated *Lm* modified to express a tumor-associated antigen enhances the induction of tumor antigen-specific T cell responses as well as delays tumor growth. Furthermore, in a recently completed clinical study performed in patients with metastatic pancreatic cancer, the sequential administration of GVAX pancreas and CRS-207 immunotherapies resulted in improved OS in patients receiving the combination compared to GVAX pancreas vaccine alone. GVAX pancreas vaccine is composed of irradiated, allogeneic pancreatic cancer cells modified to express GM-CSF and is given with a low-dose of CY to inhibit regulatory T cells. In prior studies, GVAX pancreas vaccine induced mesothelin-specific T cell responses that correlated with survival[12-15]. CRS-207 is live-attenuated, double-deleted (LADD) *Lm* modified to express the tumor-associated antigen, mesothelin. LADD *Lm* induces the release of stimulatory cytokines and is unique in its capacity to stimulate both innate and adaptive immunity by activating T cells and NK cells. LADD *Lm* is able to deliver tumor antigens directly to antigen-presenting cells in the context of the "danger signals" required to promote immunity over tolerance.

Importantly, the combination of GM-CSF whole cell vaccines with anti-CTLA-4 or anti-PD-1 shows improved responses in preclinical and clinical studies, and PD-1 antibody therapy also synergizes with *Lm*-based vaccines in murine studies[14,16-19]. In addition, preclinical data using CY in combination with GVAX, *Lm*, and PD-1 and PD-L1 blockade increase activity of these agents[20,21]. Nivolumab is a fully human monoclonal immunoglobulin (Ig) G4 antibody against PD-1 and is showing activity in multiple tumor types including melanoma, renal cell carcinoma (RCC), and non-small cell lung cancer (NSCLC)[10]. We hypothesize that the addition of nivolumab to the prime-boost vaccination regimen of CY/GVAX pancreas vaccine followed by CRS-207 will improve the survival of patients with previously treated pancreatic cancer.

The proposed timing of administration and doses of CY (200 mg/m^2), GVAX pancreas vaccine (5×10^8 cells), and CRS-207 (1×10^9 colony-forming units [CFU]) for this study have been used previously and were well tolerated[22]. The proposed dose level of nivolumab (3 mg/kg) was also tolerated in a prior Phase 1 study[10]. Preclinical data evaluating combinatorial therapy with CY/GVAX and PD-1 antibody blockade (where PD-1 blockade is administered one day prior to vaccination) demonstrated enhanced murine survival and the infiltration of IFN-γ producing $CD8^+$ lymphocytes in the tumor microenvironment[23]. This study will be the first to investigate the efficacy, immunogenicity, and safety of CY/nivolumab and GVAX pancreas vaccine therapy given in sequence with nivolumab/CRS-207 in subjects with metastatic pancreatic adenocarcinoma.

Phase 2, Randomized Trial of GVAX Pancreas Vaccine and CRS-207 Immunotherapy versus GVAX Alone in Patients with Metastatic Pancreatic Cancer. This heterologous prime-boost vaccination approach stimulates a broad immune response against pancreas tumor cells with the

GVAX pancreas vaccine and then boost the response using CRS-207 specifically targeting the mesothelin protein. In our recently completed study (clinicaltrials.gov identifier NCT01417000), 90 subjects with previously treated pancreatic cancer were randomized 2:1 to receive either 2 doses of CY/GVAX pancreas vaccine followed by 4 doses of CRS-207 (Arm A) or 6 doses of CY/GVAX pancreas vaccine (Arm B) every 3 weeks. Clinically stable subjects were offered additional 20-week courses. The primary endpoint was comparison of OS between arms. Ninety-seven percent of subjects received prior therapy and 50% received 2 or more chemotherapy regimens for metastatic disease. The full analysis set included all subjects who received at least one dose of CY. OS for all subjects treated was 6.1 months in Arm A vs. 3.9 months in Arm B (two-sided, p=0.034; HR=0.59) (**Figure 1A**). The per protocol analysis set, which included all subjects who received ≥3 doses (at least 1 dose of CRS-207 in Arm A), had OS of 9.7 months in Arm A vs. 4.6 months in Arm B (p=0.034; HR=0.53) (**Figure 1B**). Combined CY/GVAX pancreas vaccine and CRS-207 was generally well-tolerated with no treatment-related SAEs or unexpected grade 3/4 toxicities. Most common side effects were limited to vaccine site reactions related to GVAX, and transient laboratory abnormalities, fevers and rigors, associated with the CRS-207 infusion. The significant difference in OS between treatment arms met the criteria for early stopping at the interim analysis and was confirmed at subsequent analyses.

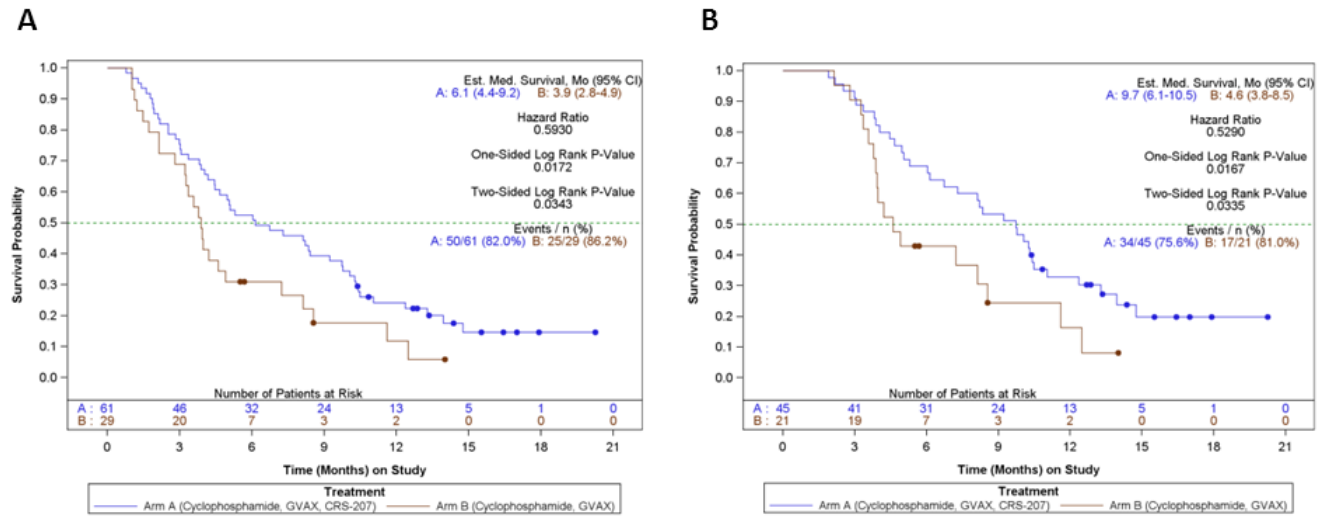

Figure 1. Overall survival favored CY/GVAX pancreas vaccine + CRS-207 over CY/GVAX pancreas vaccine alone. (A) Full analysis set. (B) Per protocol analysis set.

This combination immunotherapy resulted in extended survival for metastatic pancreatic cancer patients and serves as a promising vaccine backbone for combination with immune checkpoint blockade.

GVAX Pancreas Vaccine Induces Immune Cell Infiltration into Tumor Associated with Programmed Death-Ligand 1 (PD-L1) and PD-1 Expression. In an ongoing neoadjuvant study, GVAX pancreas vaccine is given either alone or in combination with low-dose CY. An influx of immune cells and formation of lymphoid aggregates within the tumor is induced in a majority of patients. Without the vaccine, pancreatic tumors lack significant inflammation and the T cells that exist are primarily regulatory T cells. In this study, GVAX pancreas vaccine was able to induce an influx of tumor-infiltrating lymphocytes as early as 2 weeks after vaccine

administration[24].

Figure 2 is an example of a resected tumor with lymphoid aggregates consisting of a number of cell types including B and T cells (**2A-C**). Upregulation of the PD-1 checkpoint pathway (PD-L1/PD-1) is also apparent (**2D**). These lymphoid aggregates were seen in the majority of vaccinated subjects but the number of aggregates range from 1-35/HPF. GVAX pancreas vaccine is able to generate tumor-infiltrating lymphocytes and preclinical studies suggest that combination with immune checkpoint inhibitors can release the brakes on vaccine-induced T cells [16,25,26].

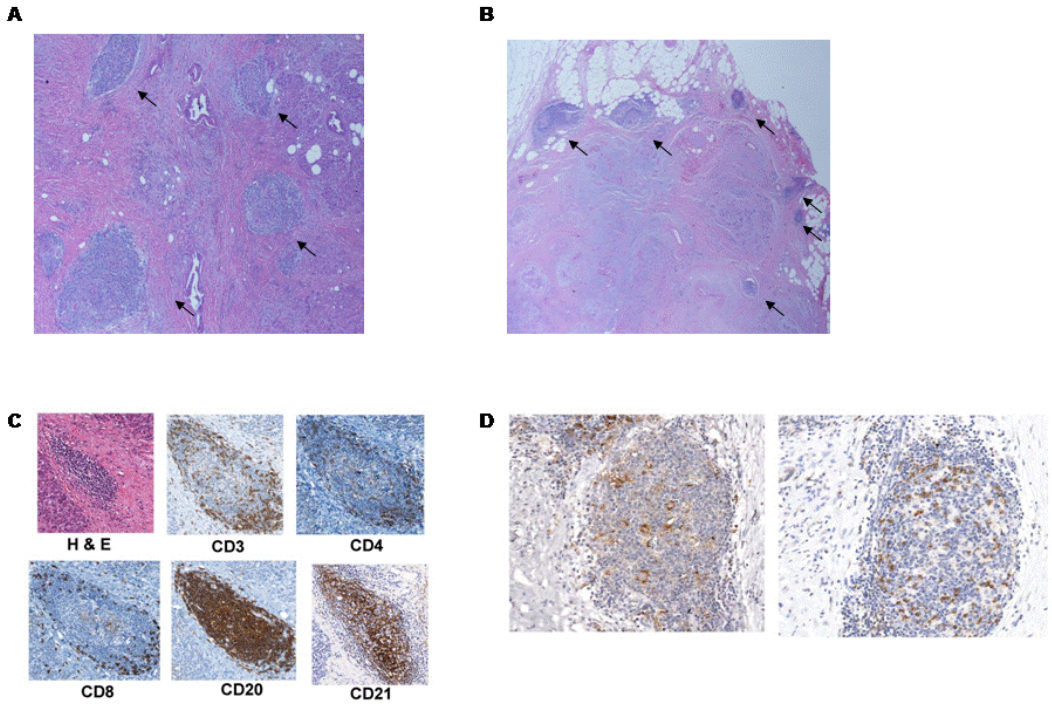

Figure 2. GVAX pancreas vaccine induces lymphoid aggregates in pancreatic tumors. **A.** Lymphoid aggregates (arrows) were found in intratumoral locations of pancreatic cancer 2 weeks after vaccination. **B**. Lymphoid aggregates (arrows) were found in peritumoral locations of pancreatic cancers from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

M2 Monocyte-Macrophage Phenotype Can Present Resistance to Immune Therapy in Pancreatic Cancer. Suppressive immune cells are not limited to regulatory T cells. Pancreatic cancer is also characterized by increased numbers of suppressive myeloid cells and tumor-associated fibrosis which typify a chronic "wound healing"/anti-inflammatory phenotype[27-29].

[redacted] (M. Gough, unpublished).

Reduction of both regulatory T cells and myeloid derivied suppressor cells in the periphery (splenic) and tumor microenvironment (conversion from M2 to M1 phenotype) are seen in preclinical tumor models treated with *Lm*-based vaccine in combination with anti-PD-1 antibody[19]. In the animal model, the vaccine is responsible for these immune cell subset changes and not particularly influenced by anti-PD-1. However, addition of anti-PD-1 significantly increases $CD8^+$ T cell intratumoral infiltrates. Characterization of the effects of *Lm*-based vaccine given in prime-boost fashion with GVAX pancreas vaccine in patients with pancreatic cancer and the impact of the addition of anti-PD-1 will be crucial for mechanistic understanding and potential immunologic predictors of tumor response.

Phase 1b Randomized Trial of Ipilimumab (IPI) versus GVAX Pancreas Vaccine + IPI in Advanced Pancreatic Cancer. GVAX pancreas vaccine has been previously combined with CTLA-4 blockade[14]. Thirty subjects with previously treated pancreatic cancer were randomized 1:1 to IPI at 10mg/kg alone (Arm 1) or in combination with GVAX pancreas vaccine (Arm 2). The higher dose of 10mg/kg of IPI was chosen because IPI at 3mg/kg in pancreatic cancer had previously been reported and demonstrated a low but detectable response rate. Studies in melanoma also suggested that the 10 mg/kg dose was more efficacious. Subjects received 4 induction doses of IPI or GVAX pancreas vaccine + IPI at 3-week intervals and then maintenance with the same treatment every 3 months. Two subjects in Arm 1 showed evidence of stable disease (7 & 22 weeks) but none demonstrated CA19-9 biochemical responses. In contrast, 3 subjects in Arm 2 had evidence of prolonged disease stabilization (31, 71, & 81 weeks) and 7 subjects experienced CA19-9 declines. In 2 of these subjects, disease stabilization occurred after an initial period of progression. The median OS (3.6 vs 5.7 months, HR: 0.51, p=0.072) and 1 year OS (7 vs 27%) favored Arm 2. Induction and maintenance of T cell responses and enhancement of the T cell repertoire directed at mesothelin correlated with OS.

Nivolumab. The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control[30]. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in various tumors[31-34]. Binding of either PD-1 ligand to PD-1 inhibits T cell activation triggered through the T cell receptor. The observed correlation of clinical prognosis with PD-L1 expression in multiple cancers suggests that the PD-1/PD-L1

pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

[redacted]

The preclinical and clinical data support that the prime-boost vaccination strategy has diverse abilities to recruit adaptive and innate immunity as well as T cell and antibody responses and makes it a promising backbone to combine with immune checkpoint blockade. Furthermore, data suggesting synergy of anti-CTLA-4 and anti-PD-1 with GVAX and anti-PD-1 with LADD *Lm* provide a strong rationale to quickly move this concept into the clinics for this rapidly fatal disease.

3. PATIENT SELECTION

3.1 Inclusion Criteria

3.1.1 Age ≥18 years.

3.1.2 Have histologically- or cytologically-proven adenocarcinoma of the pancreas. Patients with mixed histology will be excluded.

3.1.3 Have metastatic disease.

3.1.4 Have received and failed only 1 prior chemotherapy regimen for metastatic pancreatic cancer.

- Must have received and failed only 1 prior regimen administered for pancreatic cancer in the metastatic setting; failure includes development of metastases on or within 3 months of adjuvant chemotherapy treatment or development of metastases on or within 3 months of treatment for locally advanced disease or radiographic disease progression on or within 3 months of treatments for metastatic disease. Documented intolerance (grade 3 or 4 toxicity or hospitalization leading to discontinuation) of treatment for metastatic disease will also be considered a failure.
- Radiosensitizing doses of chemotherapy are not considered systemic chemotherapy

3.1.5 Patients with the presence of at least one lesion with measurable disease as defined by 10 mm in longest diameter for a soft tissue lesions or 15 mm in short axis for a lymph node by RECIST 1.1.

3.1.6 Patients acceptance to have a tumor biopsy of an accessible lesion at baseline and on treatment if the lesion can be biopsied with acceptable clinical risk (as judged by the investigator).

3.1.7 ECOG performance status 0 or 1 (**Appendix A**).

3.1.8 Life expectancy of greater than 3 months.

3.1.9 Patients must have adequate organ and marrow function as defined below:

– Leukocytes	≥ 3,000/mcL
– Absolute neutrophil count	≥ 1,500/mcL
– Platelets	≥ 100×10^3/uL
– CD4 Count	≥ 200/mcL
– Hemoglobin	≥ 9.0 g/dL
– Total bilirubin	≤ upper limit of normal (ULN) except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL
– AST(SGOT) and ALT(SGPT)	≤2.0 × ULN
– Alkaline phosphatase	≤5.0 × ULN
– Creatinine	≤1.5 × ULN or creatinine clearance (CrCl) ≥ 40 mL/min (if using the Cockcroft-Gault formula below):

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

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

- Albumin ≥3.0 g/dL

3.1.10 Women of childbearing potential (WOCBP) must have a negative serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]). WOCBP is defined in **Section 5.9.**

- WOCBP must agree to follow instructions for method(s) of contraception from the time of enrollment for the duration of treatment with study drug(s) plus 5 half-lives of study drug(s) plus 4 weeks (duration of ovulatory cycle) for a total of 23 weeks post treatment completion.

- Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug(s) plus 5 half-lives of study drug(s) plus 90 days (duration of sperm turnover) for a total of 31 weeks post-treatment completion.

- At least one barrier method of contraception must be employed by all sexually active patients (male and female), regardless of other methods, to prevent the transfer of body fluids.

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

3.2 Exclusion Criteria

3.2.1 Patient has a known history or evidence of brain metastases.

3.2.2 Patient who has had chemotherapy, radiation, or biological cancer therapy within 14 days prior to the first dose of study drug.

3.2.3 Patient has received an investigational agent or used an investigational device within 28 days of the first dose of study drug.

3.2.4 Patient is expected to require any other form of systemic or localized antineoplastic therapy while on study.

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

3.2.6 Patients who have received any non-oncology vaccine therapy used for prevention of infectious diseases including seasonal vaccinations within 28 days of study treatment. Examples include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, seasonal flu, H1N1 flu, rabies, BCG, and typhoid vaccine.

3.2.7 Patients with a history of prior treatment with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA4 antibodies, or who have received both GVAX or CRS-207 will be excluded.

3.2.8 Have used any systemic steroids within 14 days of study treatment.

3.2.9 Use more than 3 g/day of acetaminophen.

3.2.10 Patients on immunosuppressive agents (e.g., TNF pathway inhibitors, PI3 kinase inhibitors) within 7 days of study treatment.

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

3.2.12 Patient has a known allergy to both penicillin and sulfa.

3.2.13 History of severe hypersensitivity reaction to any monoclonal antibody.

3.2.14 Patient has a known or suspected hypersensitivity to GM-CSF, hetastarch, corn, dimethyl sulfoxide, fetal bovine serum, trypsin (porcine origin), yeast or any other component of GVAX pancreas vaccine or CRS-207 (e.g., glycerol).

3.2.15 Have current or prior history of infection or clinically significant adverse events (AEs) associated with an exogenous implant(s) or device(s) that cannot be easily removed.

3.2.16 Subjects who have implanted medical devices that pose high risks for colonization and cannot be easily removed (e.g., artificial heart valves, pacemakers, prosthetic joints, orthopedic screw(s), metal plate(s)) if infection occurs. Other common devices such as venous access devices (e.g., Port-a-Cath or Mediport) may be permitted as well as arterial and venous stents and dental and breast implants.

3.2.17 Have any evidence of hepatic cirrhosis or clinical or radiographic ascites.

3.2.18 Have clinically significant and/or malignant pleural effusion (pleural effusions that are not clinically significant are allowed, defined as no more than 25% fluid level of the corresponding hemithorax and stable fluid level [non-progressive] over at least 6 weeks documented radiographically).

3.2.19 Have had a new pulmonary embolism, extremity deep venous thromboembolism, or portal vein thrombosis within 2 months of study enrollment (any thrombosis within 2 months of study enrollment must be approved by the Protocol Chair and/ or Medical Monitor).

3.2.20 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.

3.2.21 History of any autoimmune disease, including but not limited to: Patients with a history of inflammatory bowel disease, including ulcerative colitis and Crohn's Disease, patients with a history of symptomatic disease (e.g., rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, autoimmune vasculitis [e.g., Wegener's Granulomatosis]); CNS or motor neuropathy considered of autoimmune origin (e.g., Guillain-Barre Syndrome and Myasthenia Gravis, multiple sclerosis). Patients with Graves or Hashimoto's disease, vitiligo, and type I diabetes mellitus will be allowed.

3.2.22 All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to grade 1 (National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE], version 4.03) or baseline before administration of study drug. Subjects with toxicities attributed to prior anti-cancer therapy which are not expected to resolve and result in long-lasting sequelae, such as neuropathy after chemotherapy, are permitted to enroll.

3.2.23 Have received a diagnosis of human immunodeficiency virus (HIV), hepatitis B or hepatitis C (patients who are hepatitis C antibody positive may be enrolled if they are confirmed with negative viral load at screening)

3.2.24 Patient has a pulse oximetry of <92% on room air.

3.2.25 Patient is on supplemental home oxygen.

3.2.26 Patient has an unhealed surgical wound.

3.2.27 Patient has clinically significant heart disease (such as uncontrolled angina, myocardial infarction within the last 3 months or congestive heart failure of New York Heart Association III or IV).

3.2.28 Patient has valvular heart disease that requires antibiotic prophylaxis for prevention of endocarditis.

3.2.29 Have insufficient peripheral venous access to permit completion of the study dosing and compliance with study phlebotomy regimen

3.2.30 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.

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

3.2.32 Patient is unable to avoid intimate contact with another individual known to be at high risk of listeriosis (e.g., newborn infant, pregnant woman, HIV-positive individual) for at least 7 days after receiving CRS-207 infusion.

3.2.33 Patient is pregnant or breastfeeding.

3.2.34 Have rapidly progressing disease, as judged by the investigator (e.g., rapid progression through prior treatment[s]).

3.3 Inclusion of Women and Minorities

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

4. RANDOMIZATION AND BLINDING

This study is an open-label study. As such, assignment of study treatment will not be blinded.

Subjects will be randomized to Arm A (CY/nivolumab/GVAX pancreas vaccine followed by nivolumab/CRS-207) or Arm B (CY/GVAX pancreas vaccine followed by CRS-207) in a 1:1 fashion. Randomization of subjects will be stratified by disease status (progressive disease [PD] or stable disease [SD]) and site at study entry.

5. TREATMENT PLAN

5.1 Agent Administration

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

Subjects on both arms will receive treatment every 3 weeks for 6 cycles of treatment within a course. A course of treatment will be 20 weeks, with 16 weeks of treatment followed by an end-of-course (EOC) evaluation approximately 4 weeks after the last study treatment administration in the course. At the investigator's discretion, all subjects may receive additional courses of the assigned treatment regimen if they are clinically stable and meet dosing eligibility criteria. Treatment Arm A will include 2 cycles of CY/nivolumab/GVAX pancreas vaccine, followed by 4 cycles of nivolumab/CRS-207. Treatment Arm B will include 2 cycle of CY/GVAX pancreas vaccine followed by 4 cycle of CRS-207.

Table 1: Treatment Schedule

TREATMENT SCHEDULE				
Arm	**CY**	**Nivolumab**	**GVAX**	**CRS-207**
A	Day 1, Cycles 1, 2	Day 1, Cycles 1, 2, 3, 4, 5, 6	Day 2, Cycles 1, 2	Day 2, Cycles 3, 4, 5, 6
B	Day 1, Cycles 1, 2	None	Day 2, Cycles 1, 2	Day 1, Cycles 3, 4, 5, 6

Table 2: Regimen Description

REGIMEN DESCRIPTION				
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Course Length***
CY	Subjects may be pre-medicated with anti-emetics prior to CY administration.	200 mg/m^2 in 100ml NS	IV infusion over 30 min*	20 weeks
GVAX	EMLA cream (approximately 2.5 grams per site, at least 1 hour prior to vaccination)	5×10^8 cells	Six intradermal injections	
CRS-207	650 mg acetaminophen; 500ml NS pre-infusion; 1000ml NS post-infusion	1×10^9 CFU in 250ml NS	IV infusion over 2 hours*	
Nivolumab	No prophylactic pre-medication will be given unless indicated by previous experience in an individual subject per **Section 5.3.4**.	3 mg/kg	IV over 60 minutes*	

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

Please see **Section 6.2** for guidance regarding dosing delays. Subjects that are required to stop treatment with nivolumab due to toxicity may continue to receive CY/GVAX pancreas vaccine followed by CRS-207 (assessment schedule per **Section 10.2**).

5.1.1 Cyclophosphamide (CY)

Subjects may be pre-medicated prior to administration with anti-emetics per institutional guidelines. Subjects on Arm A should be observed for 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 Protocol Chair and/or Medical Monitor and 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.

5.1.2 GVAX Pancreas Vaccine

[redacted]

5.1.3 CRS-207

[redacted]

5.1.4 Nivolumab

[redacted]

[redacted]

5.2 Dosing Criteria

Dosing of study therapy will be delayed for the following laboratory criteria:

- AST/ALT >3 × ULN
- Total bilirubin > 1.5 x ULN or direct bilirubin > 2.0 × ULN for subjects with Gilbert's disease
- Creatinine > 1.5 × ULN
- Hemoglobin < 8 g/dL
- ANC < 1000/uL
- Platelets < 80 × 10^3/uL

Please see **Section 6.2** for further guidance regarding dosing delays.

5.3 General Concomitant Medication and Supportive Care Guidelines

5.3.1 Cyclophosphamide (CY)

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

5.3.2 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.

5.3.3 CRS-207

Guidance on treatment of the common infusion reactions related to CRS-207 dosing is as follows:

- **Fevers:** Despite the acetaminophen premedication, subjects can spike fevers up to 40°C starting at the end of the CRS-207 infusion generally through the next 24 hours. Oral ibuprofen (400 to 800 mg) and acetaminophen (650 to 1000 mg) may be used in alternate sequence every 4 hours.

- **Rigors**: Rigors (generally once or twice per infusion) have been observed to start during or at the end of a CRS-207 infusion through 24 hours. IV narcotics such as morphine or meperidine may be administered per institutional policy. Oral morphine or non-steroidal anti-inflammatory drugs (NSAIDs) (e.g., aspirin, ibuprofen, naproxen) may be used as home treatment.

- **Blood pressure**: Decreases in blood pressure have been observed necessitating additional IV fluids during the 4 hour observation period (up to 1 or 2 liters). Reasons for this include the development of fever, compartmental shifts of fluid resulting from the CRS-207 infusion and the use of narcotics. Some subjects have also been slightly hypotensive at 24 hours upon arrival to the clinic after CRS-207 administration. Subjects are encouraged to hydrate themselves liberally at home with oral fluids.

- **Nausea and vomiting**: Nausea and vomiting have been reported and observed within 24 hours after CRS-207 infusion. Subjects may be given anti-emetics as needed.

Blood draws for clinical hematology and serum chemistry will be done the day after the CRS-207 infusion. Any unexpected grade 3 or greater laboratory abnormalities should be repeated within 24-72 hours.

5.3.4 Nivolumab

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

5.3.4.1 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 Protocol Chair and/or Medical Monitor and BMS and reported as an SAE if 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 acetaminophen 325 to 1000 mg 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 acetaminophen 325 to 1000 mg; 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, 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 case report form (CRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg should be administered at least 30 minutes before additional nivolumab administrations.

For grade 3 or grade 4 symptoms (severe reaction, grade 3: prolonged [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]; grade 4: (life threatening; pressor or ventilator 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 (e.g., appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).

Please refer to **Section 6.2** for guidelines regarding GVAX and CRS-207 treatment delays following a nivolumab infusion-related reaction.

5.3.4.2 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 or SAE CRF. Identification and treatment of nivolumab-related AEs can be found in **Appendix B**. Additional guidance can be found in the nivolumab Investigator's Brochure (IB). Antibiotics will also be administered to subjects who have not yet received antibiotics for CRS-207 and the subject requires steroids for a suspected nivolumab-related AE. (**Section 5.6**).

Subjects who experience a grade 2 or higher nivolumab-related AE should be discussed with the Protocol Chair and/or Medical Monitor and IND sponsor immediately.

5.4 Prohibited and/or Restricted Medications and Devices

The following therapies or devices are not permitted during the treatment period (if administered, the subject may be removed from the study):

- Any non-study anticancer chemotherapy or immunotherapy (approved or investigational)
- TNF pathway inhibitors or PI3 kinase inhibitors
- Systemically active steroids can be used but should be reported to the Protocol Chair and/or Medical Monitor and IND Sponsor. Steroid treatment should be completed at least 14 days prior to resuming study-related treatments.
- Another investigational agent
- Filgrastim (Neupogen® or G-CSF) or sargramostim (Leukine® or GM-CSF)
- Prophylactic vaccines (e.g., influenza, pneumococcal, Td/Tdap) within 28 days prior to or after dosing
- 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.
- Implanted medical devices that pose high risks for colonization and cannot be easily removed (e.g., artificial heart valves, pacemakers, prosthetic joints, orthopedic screw(s), metal plate(s)) if infection occurs are prohibited. Other common devices such as venous access devices (e.g., Port-a-Cath or Mediport), arterial and venous stents, and dental and breast implants may be permitted if approved by the Protocol Chair and/or Medical Monitor.

In addition, the following therapies should not be administered during the treatment period unless medically necessary and approval must be obtained from the Protocol Chair and/or Medical Monitor for a subject to continue dosing if therapy is given concurrently with study participation:

- General anesthesia or deep sedation
- Aspirin >325 mg/day (chronic daily use of aspirin ≤325 mg/day and heparin flushes for central lines are allowed)
- More than 4 g/day of acetaminophen
- Systemic antibiotics

5.5 Other Restrictions and Precautions

Palliative (limited-field) radiation therapy is permitted, but only for pain control to sites present at baseline and with approval by the Protocol Chair and/or Medical Monitor or IND Sponsor.

5.6 Antibiotic Administration [redacted]

[redacted]

Should a patient require emergent implant of a prohibited device (as described in **Section 5.4**) while on therapy, the patient will receive a 14-day IV antibiotic regimen appropriate for the coverage of wild-type listeriosis.

Antibiotics will also be administered to subjects who have not yet received antibiotics for CRS-207 and the subject requires steroids for a suspected nivolumab-related AE. Antibiotic prophylaxis should be given for the duration of the treatment with the steroid (recommended oral 80 mg trimethoprim / 400 mg sulfamethoxazole once daily or 160 mg trimethoprim / 800 mg sulfamethoxazole (DS) three days a week).

[redacted]

[redacted]

Subjects with clinical or laboratory signs or symptoms of infection who require initiation of antibiotics other than specified by protocol should have a clinically-relevant evaluation, including appropriate bacterial cultures. Culture of cerebrospinal fluid should be obtained for subjects with suspected central nervous system infection. In such instances, analysis of cerebrospinal fluid should also include cell count, protein, glucose and Gram stain. IV ampicillin (or trimethoprim/sulfamethoxazole in penicillin-allergic subjects) plus gentamicin should be initiated for possible infectious complications of CRS-207 for subjects who are suspected of having CRS-207 infection and meet the criteria listed below:

- Flu-like symptoms Grade 3 or greater lasting for ≥12 hours
- Fever Grade 4 or higher (>40.0ºC for >24 hours)
- Persistent fever >39ºC lasting for ≥48 hours
- Infection Grade 3 or higher (infection with interventional radiology or operative intervention indicated)
- Evidence of abscess
- Clinical signs or symptoms (e.g., neurologic signs or symptoms), which, in the judgment of the investigator, necessitate starting antibiotics

[redacted]

Suspected or confirmed infection with CRS-207 and/or Listeria is considered an adverse event of special interest (AESI) and should be reported following SAE reporting procedures (**Section 7.1.3**) irrespective of temporal relationship to study drug administration. This includes scheduled blood cultures during surveillance monitoring that are positive for CRS-207 or if a subject presents with symptoms suspicious for a Listeria-like infection and/or is tested positive for Listeria at a local hospital/clinic.

5.7 Definition of an Overdose for this Protocol

Overdose of nivolumab is defined as:
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 (see **Section 7.5.1** for reporting details). Appropriate supportive treatment should be provided if clinically indicated.

All reports of overdose with and without an AE must be reported within 24 hours to the Protocol Chair and / or Medical Monitor, IND Sponsor (Dr. Elizabeth Jaffee), Aduro Biotech, Inc. (Aduro), and Bristol-Myers Squibb (BMS). IND Sponsor, Aduro, and BMS contact information can be found in **Section 7.5.1**.

5.8 Unacceptable Toxicity

Unacceptable toxicities are defined as treatment-related ≥ grade 4 AEs, or treatment-related grade 3 AEs not improving to ≤ grade 2 under therapy within 2 weeks. Exceptions include:

- Asymptomatic amylase and lipase elevation
- Grade 3 or 4 lymphopenia or hypophosphatemia
- ≥ 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.

[redacted]

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

The proportion of unacceptable toxicities will be monitored. If the toxicity levels in Treatment Arms A or B are unacceptable (>33% of subjects), then enrollment will be suspended until further review and consideration by the Protocol Chair and / or Medical Monitor, IND Sponsor, and the DMC. There will be no dose reductions for CY, nivolumab, CRS-207, or GVAX pancreas vaccine.

The proportion of treated subjects with unacceptable toxicity will be monitored using a Bayesian stopping guideline. A Beta (1.5, 5.5) prior, representing a toxicity rate of 21%, a slightly conservative estimate, was used in the development of our guidelines. The therapy will be re-evaluated if the posterior probability that the toxicity rate exceeds the 33% boundary is greater than 50%. Toxicity will be monitored continuously. Table 3 summarizes the stopping boundaries for unacceptable toxicities.

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

Number of Subjects Per Treatment Arm	Number of toxicities needed to trigger re-evaluation
6	3
7-9	4
10-12	5
13-15	6
16-18	7
19-21	8
22-24	9
25-27	10
28-30	11
31-33	12
34-36	13
37-39	14
40-42	15
43-45	16
46-48	17
49-51	18
52-54	19

The probability of triggering the stopping guidelines was assessed for a range of possible true toxicity rates using simulations with 10,000 replicates (Table 4). The probability of stopping to re-evaluate was 7.3% if the true proportion with an unacceptable toxicity was 15%. In comparison, the probability of stopping early is 72.6% if the true proportion with an unacceptable toxicity was 33%.

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

True probability of unacceptable toxicity	Probability of triggering stopping guidelines
1%	<0.1%
5%	0.2%
10%	2.1%
15%	7.3%
20%	18.2%
25%	35.9%
30%	57.5%
33%	72.6%
35%	79.3%

5.9 WOCBP, Contraception, Use in Pregnancy, Use in Nursing

A WOCBP is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, women under the age of 62 years must have a documented serum follicle stimulating hormone (FSH) level > 40mIU/mL to confirm menopause.*

*Women treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgment in checking serum FSH levels. If the serum FSH level is >40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal:

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

5.9.1 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 (defined as a woman who is > 45 years of age and has not had menses for greater than 12 months and women under the age of 62 must have a documented serum follicle stimulating hormone (FSH) level less than 40mlU/mL 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) 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 23 weeks after the last dose of study drug. Male subjects enrolled in this study must also agree to use an adequate method of contraception starting with Visit 1 through 31 weeks 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
- Tubal ligation
- 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 drug 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.

5.9.2 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. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated.

Pregnancy in female subjects throughout the study or within 23 weeks of completing treatment as well as any pregnancy in partners of male subjects throughout the study or within 31 weeks of completing the study should be reported initially as a serious adverse event (see SAE reporting procedures in section 7.5.1 and 7.5.5) by the investigator within

24 hours of learning of its occurrence. Pregnancy information must be reported on the Pregnancy Form.

Protocol required procedures for study 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 any voluntary or spontaneous termination, perinatal and neonatal outcome and where applicable, offspring information must be reported on the Pregnancy Follow-up Form. Pregnancy outcomes must also be collected for the female partners of any males in this trial. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

5.9.3 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.

5.9.4 All Subjects (Male and Female)

All sexually active patients must use at least a barrier method (i.e., condom) to prevent transmission of body fluids.

5.10 Duration of Therapy

Subjects who are clinically stable and meet dosing requirements (per **Section 5.2**) at the end of the first course may receive additional courses of their assigned treatment based on investigator discretion. The additional course(s) may start as early as 4 weeks from last dose of previous course and all assessments will be followed per the study schedule in **Section 10**, with the first dose of the additional course corresponding to Day 1, Cycle 1 of the study schedule. The following assessments are not required during additional courses:

- HLA-typing
- Tumor biopsies
- Stool samples for microbial biomarker analyses
- Whole blood for isolation of PBMCs except during Cycle 4 (Day 1 only) and Cycle 6
- Whole blood draw for *Lm*- and mesothelin-specific immunity assays except during Cycle 4 and Cycle 6

Assessments done at End of Course (EOC) which are required at Day 1, Cycle 1 do not need to be performed if the next course is started within 14 days of the EOC visit assessments.

5.11 Criteria for Removal from Treatment

The reason for study removal and the date the subject was removed will be documented in the CRF. A subject will be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent for participation in the study.

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent for treatment
- Intercurrent illness that prevents further administration of treatment
- Unacceptable toxicity (see **Section 5.8**)
- Disease progression as defined in **Section 5.11.1**
- Severe or life-threatening nivolumab-related AE(s) (see **Section 5.11.2**)
- Need for >2 dose delays due to the same toxicity as per the dose delay guidelines (see **Section 6.2**)
- If, in the opinion of the Investigator, a change or temporal or permanent discontinuation of therapy would be in the best interest of the subject,
- Noncompliance with trial treatment or procedure requirements,
- Subject is lost to follow-up
- Subject becomes pregnant

5.11.1 Disease Progression

GVAX pancreas vaccine, CRS-207, and nivolumab are expected to trigger immune-mediated responses, which require activation of the immune system prior to the observation of clinical responses. Such immune activation may take weeks to months to be evident. Some subjects may have objective volume increase of tumor lesions or other disease parameters within weeks following the start of immunotherapy. Such subjects may not have had sufficient time to develop the required immune activation or, in some subjects, tumor volume or other disease parameter increases may represent infiltration of lymphocytes into the original tumor. In conventional studies, such tumor volume or relevant laboratory parameter increases during the first 2-4 months of the study would constitute disease progression and lead to discontinuation of imaging to detect response, thus disregarding the potential for subsequent immune-mediated clinical response. This phenomenon was observed in approximately 10% of subjects in the Phase 1 study of nivolumab and has also been reported for ipilimumab monotherapy[35].

Subjects will be permitted to continue with treatment beyond initial RECIST 1.1 defined PD as long as they meet the following criteria:

- Investigator-assessed clinical benefit, and
- Subject is tolerating study drug.

The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment. The following criteria need to be taken into consideration:

- Absence of clinical symptoms and signs indicating disease progression.
- No decline in ECOG performance status.
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

All decisions to continue treatment beyond PD must be discussed with the Protocol Chair and / or Medical Monitor and documented in the study records.

Tumor assessments will be made using RECIST 1.1 (**Appendix C**) and irRC (**Appendix D**).

5.11.2 Nivolumab-Related Adverse Events

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, Aduro, 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
    - 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 (applies to nivolumab only) of any duration requires discontinuation
        - Grade 3 treatment-related laboratory abnormalities do not require treatment discontinuation except:
            - Grade 3 treatment-related thrombocytopenia 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. It is recommended to consult with the Protocol Chair or Medical Monitor for grade 4 amylase or lipase abnormalities.

- Isolated grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management.

- Transient, self-correcting grade 4 AST or ALT that occur after the CRS-207 infusion and resolves within 2 weeks.

- Grade 4 lymphopenia.

- Any dosing interruption lasting > 6 weeks with the following exceptions:

  - Dosing interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Protocol Chair and/or Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.

  - Dosing interruptions > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the Protocol Chair and/or Medical Monitor. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Protocol Chair or Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.

Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.

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 that are required to stop treatment with nivolumab due to toxicity may stay on study and receive CY/GVAX pancreas vaccine followed by CRS-207 (assessment schedule per **Section 10.2**) once the nivolumab-related toxicity(s) has resolved to a grade 1.

5.12 End of Course (EOC)/End of Treatment (EOT)/Safety Follow-up Visit

At the investigator's discretion, subjects may receive additional courses of the assigned treatment regimen if they are clinically stable and meet dosing eligibility requirements, as determined at an EOC evaluation 4 weeks after completion of each course of therapy. The EOC visit may be

conducted several times during the study if a subject completes more than one course of drug therapy. All subjects will return to the study site approximately 4 weeks (± 7 days) after the last infusion of study drug (i.e., completion of the final course or upon early discontinuation) for an EOT evaluation. Procedures and assessments performed at these visits and beyond should follow the respective guidelines described in **Sections 5.13 and 10.0** as appropriate. Note: If it is determined at an EOC visit that the subject will not move on to additional courses then the EOT visit can be conducted at the same time. Assessments for EOC and EOT are the same, as described in **Section 10.0**.

The EOT visit is conducted only once after the final study treatment. If the EOT visit occurs early (e.g., 1 week prior to the expected visit as protocol allows), an assessment for AEs should be made by telephone or email on day 28 (± 1 day) after last dose of study drug and documented.

[redacted]

The subject will be monitored for AEs up to the mandatory EOT/Safety Follow-Up Visit or to resolution of toxicity to ≤ Grade 1, whichever occurs later. SAEs that occur within 100 days (+14 day reporting window) of last dose of nivolumab for subjects in Arm A (or for 28 days from the last dose of cyclophosphamide, GVAX, or CRS-207 if the subject is no longer receiving nivolumab due to toxicity, whichever reporting period is longer) or within 28 days of last dose of study drug for subjects in Arm B, and before initiation of a new antineoplastic treatment (whichever comes first) should also be followed and recorded.

5.13 Duration of Follow-Up

All randomized subjects, including those never treated, will enter a follow-up period. Treated subjects will begin the follow-up period after they complete the EOC/EOT / Safety Follow-Up Visit. Subjects will be contacted every 12 weeks (and at 100 days [+14 days] from the last dose of nivolumab for subjects in Arm A if the subject was still receiving nivolumab at the time of treatment discontinuation) to monitor Overall Survival until death, withdrawal of consent, or study closure. Information of other cancer therapies after discontinuation from the study treatment will be collected.

All subjects should continue to be monitored for disease status by radiologic imaging. Disease monitoring should continue to be assessed every 12 weeks until, 1) start of a new antineoplastic therapy (information of the new cancer therapy will be collected), 2) until death, 3) withdrawal of consent, or 4) study closure, whichever occurs first.

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

All subjects will be followed for at least 4 weeks after their last dose of study drug for the development of AEs. SAEs that occur within 100 days (+14 day reporting window) after the last dose of nivolumab for subjects in Arm A or within 28 days (+7 day reporting window) from the last dose of cyclophosphamide, GVAX, or CRS-207, if the subject never received nivolumab or

is no longer receiving nivolumab due to toxicity (whichever reporting period is longer) should be followed and recorded. SAEs that occur within 28 days (+7 day reporting window) after last dose of study drug for subjects in Arm B, or until initiation of a new antineoplastic treatment should also be followed and recorded.

At the conclusion of the study, all remaining 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. Subjects who are still receiving treatment at the time of study close may complete the current treatment course (up to 6 cycles) and EOT/Safety Follow-Up Visit prior to transitioning to participation in the separate long-term follow-up study.

[redacted]

[redacted]

5.14.1 Confirmed Listeria Infection

In the event a subject has a positive Listeria culture at any time during or after study participation (except within 7 days after a CRS-207 infusion), the IND Sponsor and Aduro should be notified within 24 hours of the adverse event of special interest (AESI) per **Section 7.1.3**.

If Listeria has been confirmed at the clinical site or an external laboratory, all efforts should be made to obtain a sample of the bacterial isolate from the original positive culture and submit to Aduro for strain confirmation; records on all samples cultured during this period must be obtained and provided to the Sponsor. Refer to the Central Laboratory Manual for sample collection and shipping instructions.

5.14.2 Suspected Infection with CRS-207 or Listeria

In the case of a suspected persistent CRS-207 or Listeria infection that has not been confirmed by culture, collection of blood, urine and stool samples in duplicate is recommended. One set of samples should be cultured locally for Listeria per institutional guidelines. Culture of cerebrospinal fluid should be obtained for subjects with suspected central nervous system infection. In such instances, analysis of cerebrospinal fluid should also include cell count, protein, glucose, and Gram stain. If samples are positive for Listeria, the IND Sponsor and Aduro must be notified immediately, and the duplicate samples and Listeria isolate must be sent to Aduro or designee for testing to confirm CRS-207. Instructions on collection, storage and shipping of samples for CRS-207 testing are provided in the Central Laboratory Manual.

6. DOSING DELAYS/DOSE MODIFICATIONS

6.1 Dose Modifications

Dose reduction or dose increase of CY, GVAX pancreas vaccine, CRS-207 and nivolumab will not be permitted.

6.2 Dosing Delays

All scheduled cycles within a course are to be given approximately 3 weeks apart. If necessary, a scheduled cycle may be delayed for up to 1 week. In this case, subsequent cycles should continue so that a subject can still receive all 6 cycles given that the cycles are a minimum of 3 weeks apart and they have not experienced an AE necessitating discontinuation. If delayed more than 1 week, the Protocol Chair and/or Medical Monitor must be contacted for further instructions on continued treatment. Additional delays or modifications to the treatment schedule must be approved by the Protocol Chair and / or Medical Monitor or IND Sponsor.

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

- Nivolumab-related infusion reactions must resolve to baseline prior to administration of either GVAX or CRS-207.
- Resume Day 2 treatment schedule (GVAX or CRS-207) and assessments without repeating Day 1 study treatments (CY and/or nivolumab) if the delay is within 72 hours.
- If the delay is longer than 72 hours, repeat Day 1 and Day 2 (if applicable) study treatments/assessments with a minimum of 1 week (Treatment Arm B) or 2 weeks (Treatment Arm A) from the previous Day 1 treatment. This includes steroid treatment requiring at least a 14 day washout prior to resuming study-related treatments.

Nivolumab administration should be delayed for the following:

- Any grade $\geq$ 2 non-skin, treatment-related AE, with the following exceptions:
  - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
  - Grade 2 hypothyroidism or thyroiditis
- Any grade $\geq$3 skin treatment-related AE
- Any $\geq$ grade 3 treatment-related laboratory abnormality, with the following exceptions for asymptomatic amylase or lipase:
  - Grade 3 or 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations, or radiographic signs of pancreatitis do not require a dose delay. It is recommended to consult with the Protocol Chair and/or Medical Monitor for grade 3 amylase or lipase abnormalities.
  - Isolated grade 3 or 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study drug.

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
- Subjects may resume treatment in the presence of grade 2 AST/ALT OR grade 1 total bilirubin. Subjects with combined grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (**Section 5.11.2**) should have treatment permanently discontinued.
- 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 hypothyroidism and thyroiditis.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

This study will use the descriptions and grading scales found in the revised CTCAE version 4.03 for AE reporting that can be found at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

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

All AEs and SAEs experienced by subjects will be collected and reported from the first dose of the investigational agent, throughout the study, and will only be followed for 4 weeks unless related to the investigational agent. For all subjects in Arm A, all SAEs that occur either within 100 days (+14 day reporting window) after the last dose of nivolumab or for 28 days (+7 day reporting window) from the last dose of cyclophosphamide, GVAX, or CRS-207, if the subject is no longer receiving nivolumab due to toxicity, whichever reporting period is longer. All SAEs will be collected for 28 days (+7 day reporting window) after the last dose of study drug for subjects in Arm B, or until initiation of a new anti-cancer treatment, whichever occurs first.

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

Subjects who experience a grade 2 or higher nivolumab-related AE should be discussed with the Protocol Chair and / or Medical Monitor.

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 AEs. A grade 1 or 2 clinical laboratory abnormality should be reported as an AE only if it is considered clinically significant by the investigator.

7.1 Definitions

7.1.1 Adverse Event

An AE 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 AEs if they worsen after starting the study treatment (any procedures specified in the protocol). New medical conditions / diseases occurring before starting the study treatment but after signing the informed consent form will not be recorded as AEs.

Expected progression of the disease being studied will not be recorded as an adverse event; however, all deaths from time of first administration of study drug through 100 days (+14 day reporting window) after the EOT for subjects in Arm A and 28 days (+7 day reporting period) after the EOT for subjects in Arm B or before initiation of a new antineoplastic treatment (whichever comes first), regardless of causality or whether subjects have discontinued earlier from treatment, are to be reported as SAEs. Deaths that occur after 100 days of the EOT for subjects in Arm A and 28 days after the EOT for subjects in Arm B or before initiation of a new antineoplastic treatment (whichever comes first), must be reported as SAEs if they are considered related to study drug.

Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms or require therapy.

7.1.2 Serious Adverse Event

A SAE is an undesirable sign, symptom or medical condition which:

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

- 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 new cancer (that is not a condition of the study)
- Is associated with an overdose
- 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 SAEs are hospitalizations for:

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

7.1.3. Adverse Events of Special Interest

Suspected infection with CRS-207 and/or Listeria are considered adverse events of special interest (AESI) and should be reported following SAE reporting procedures in **Section 7.5** irrespective of temporal relationship to study drug administration.

In the event a subject has a positive Listeria culture at any time during or after study participation (except within 7 days after a CRS-207 infusion), the event should be reported to the Sponsor within 24 hours of the event.

All AESIs must be reported for the duration of the study regardless of causality.

7.2 Assessment of Causality

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

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

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

The following factors should also be considered:

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

Assessment of Grade:

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

7.3 Expectedness

Unexpected AE: An AE, which varies in nature, intensity or frequency from information on the investigational drug/agent provided in the product IB, package insert or safety reports. Any AE that is not included in the IB consent is considered "unexpected".

Expected (known) AE: An AE, which has been reported in the IB. An AE is considered

"expected", only if it is included in the IB document as a risk.

7.4 Handling of Expedited Safety Reports

In accordance with local regulations, the IND Sponsor or designee will notify investigators of all SAEs that are unexpected (i.e., not previously described in the IB), and related to CY, GVAX pancreas vaccine, CRS-207, 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.

7.5 Reporting

7.5.1 Adverse Events and Serious Adverse Events

All AEs (both expected and unexpected) will be captured on the appropriate study-specific CRFs. **Report AEs to the Protocol Chair and/or designee within 24 hours once identified as an unacceptable toxicity.**

All SAEs and AESIs occurring from the first dose of the study drug, throughout the study, and 100 days (+14 day reporting window) after the EOT for subjects in Arm A and 28 days (+7 day reporting window) after the EOT for subjects in Arm B or before initiation of a new antineoplastic treatment (whichever comes first) must be reported. All SAEs that the investigator considers related to study drug occurring after the follow-up periods must be reported.

To report a SAE, complete the AE form electronically in the electronic data capture (EDC) system for the study **within 24 hours** of the knowledge of the occurrence. When the form is completed, the IND Sponsor, Aduro, BMS, and Medpace Safety will be notified electronically of the event. If the event meets serious criteria and it is not possible to access the internet, send an email to Medpace Safety at [redacted] or call the Medpace SAE hotline (phone number listed below), and fax the completed paper Back-Up SAE form to Medpace (fax number listed below) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

[redacted]

7.5.2 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

Within 24 hours of receipt of follow-up information, the investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (e.g., subject discharge summary or autopsy reports) to Medpace Clinical Safety via fax or e-mail. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

7.5.3 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.

7.5.4 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 under the seriousness category checked as 'other medically important event'. Potential drug induced liver injury is defined as:

1) ALT or AST elevation > 3 times upper limit of normal (ULN)
   AND
2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
   AND
3) 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.

7.5.5 Pregnancy Reporting

Although pregnancy and lactation are not always serious by regulatory definition, 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 23 weeks of completing the trial as an SAE. This also includes the pregnancy of a male subject's female partner who has provided written consent to provide information regarding pregnancy, which occurs during the trial or within 31 weeks of completing the trial.

If a subject or partner of a subject participating in the study becomes pregnant, the investigator must report the pregnancy within 24 hours of discovery or knowledge of the event. To report a pregnancy, complete the AE form electronically in the EDC system for the study, with the seriousness category checked as 'other important medical event'. When the form is completed, the IND Sponsor, Aduro, BMS, and Medpace Safety will be notified of the event. Medpace Safety will then forward the Pregnancy Form to the investigator for completion.

All subjects or partners of subjects who become pregnant must be followed to the completion/termination of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the investigator should notify Medpace Safety. At the completion of the pregnancy, the investigator will document the outcome of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must also be reported as SAEs (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported to Medpace Safety or the IND sponsor (if the trial has completed).

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

Participating sites will be responsible for reporting to their IRB and IBC. All SAEs will be reported to the IRB and IBC per institutional guidelines if the event is related and expected, related and unexpected, or related and fatal or life-threatening due to administration of the investigational product. If the SAE is unrelated to administration of the investigational agents, then it will be reported to the IRB and IBC per institutional guidelines. Follow-up information will be submitted to the IRB and IBC as soon as relevant information is available.

7.5.7 Food and Drug Administration (FDA)

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

7.5.7.1 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 analyzed. The new report should contain comments on the significance of the new event in light of the previous, similar reports.

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

7.5.7.2 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.

7.5.8 Recombinant DNA Advisory Committee (RAC)

Unexpected SAEs believed to be related to the investigational product(s) will be reported to RAC by email if fatal or life-threatening within 7 calendar days or by written report if related and unexpected to the investigational product(s) within 15 calendar days. SAEs that are unrelated or related and expected with the investigational product (s) will be reported to RAC in the Annual Report. Follow-up information will be submitted to the RAC as soon as relevant information is available.

8. PHARMACEUTICAL INFORMATION

8.1 Cyclophosphamide (Cytoxan®, CY)

8.1.1 Agent Accountability

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

8.1.2 Mode of Action

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

8.1.3 Description

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

8.1.4 Packaging and Labeling Information

CY is commercially available.

8.1.5 Preparation

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

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

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

1. CY constituted with 0.9% sterile sodium chloride may be infused without further dilution.
2. CY constituted with 0.9% sterile sodium chloride may be infused following further dilution in the following:

    - Dextrose Injection, USP (5% dextrose)
    - Dextrose and Sodium Chloride Injection, USP (5% dextrose and 0.9% sterile sodium chloride)
    - 5% Dextrose and Ringer's Injection
    - Lactated Ringer's Injection, USP
    - Sodium Chloride Injection, USP (0.45% sterile sodium chloride)
    - Sodium Lactate Injection, USP (1/6 molar sodium lactate)

8.1.6 Storage

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

8.1.7 Stability

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

8.1.8 Route of Administration

CY is administered by IV injection over 30 minutes.

8.1.9 Subject Care Implications

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

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

CY may interfere with normal wound healing.

8.1.10 Returns and Reconciliation

N/A

8.2 GVAX Pancreas Vaccine

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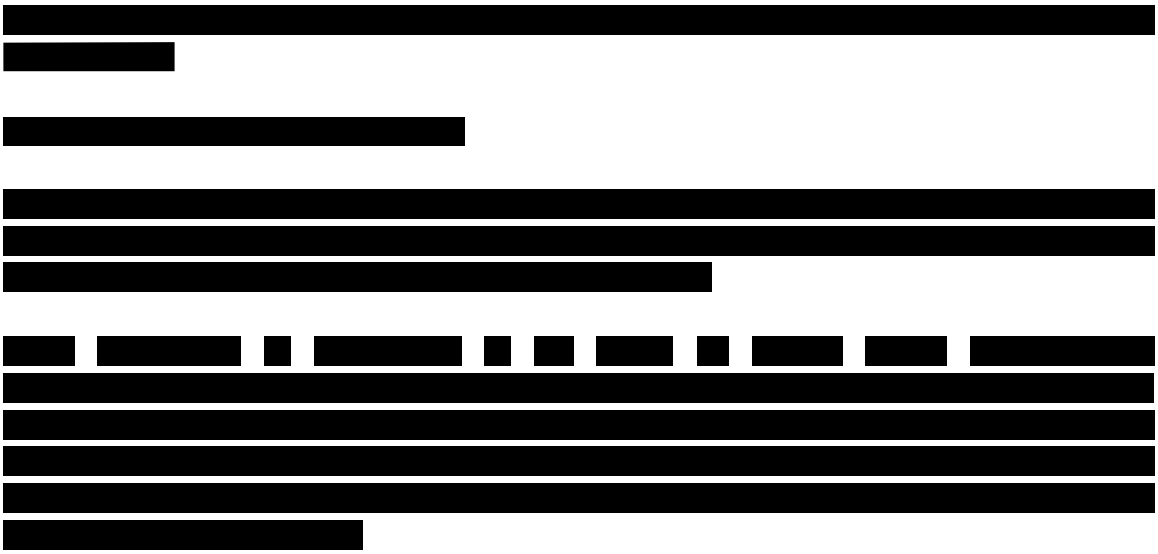

9. CORRELATIVE/SPECIAL STUDIES

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

9.1 Tumor Tissue Studies

Tumor biopsies will be collected (if a subject's tumor is thought to be reasonably safe and easy to biopsy) at baseline and at Cycle 4 (4-6 cores per timepoint). Fine needle aspiration will not be acceptable. Additional optional biopsies may be obtained later in the course of study treatment. Archival tumor samples will also be collected for every subject. Detailed instructions for tissue collection, processing and shipment will be provided in the Laboratory Manual.

To explore the association of OS, PD-L1 positivity, and tumor-infiltrating lymphocyte characteristics with clinical responses, archived tumor tissue and tumor tissue obtained at baseline and during treatment (Cycle 4) will be compared. PD-L1 expression may predict response to anti-PD-1[10,11]. However, PD-L1 is also upregulated in response to IFN-γ released by infiltrating T cells and could potentially be a predictor of response to any active immunotherapy. Pre- and post-treatment tumor biopsies will also be analyzed for PD-1 expression as well as infiltration of immune cells (effector T cells, Tregs, B cells, dendritic cells, etc). Characterization of immune checkpoint expression as well as immune infiltrates may be predictive of response to therapy and may also give insight into next generation combinatorial approaches. Preliminary data from a pancreatic cancer immunotherapy study suggests that induction of a $T_h1$and T_h17 phenotype at the tumor itself predicts response. Furthermore, upregulation of other inhibitory molecules such as IL-10 and TGF-β may identify other targets for combinatorial strategies.

Attempts will be made to obtain archived tissue samples from all subjects.

9.2 Peripheral Blood Mononuclear Cells (PBMCs)

Whole blood for isolation of PBMCs will be collected prior to dosing on Day 1 of Cycle 1, Day 1 of Cycles 3-6, and the EOC/EOT evaluation. Additionally, subjects will have whole blood for isolation of PBMCs drawn 7 days post-CRS-207 infusion of Cycles 3 and 4 (volume split between pre-dose and 7-day draw) during the first course of treatment only. Subjects receiving additional treatment courses will only have whole blood for isolation of PBMCs drawn during Cycle 4 and Cycle 6. Pre- and post-treatment changes in PBMCs including effector, helper, and regulatory T cells, NK cells, and macrophages will be measured.

The cellular immune responses directed against *Lm* and mesothelin will be evaluated by using enzyme-linked immunosorbent spot (ELISPOT) and intracellular cytokine staining. Post-treatment expression of PD-1 and other lymphocyte activation markers will be measured as well. These responses will be correlated with OS. PBMCs are isolated and stored frozen (liquid nitrogen) until use. Detailed instructions for processing and storage are provided in the Laboratory Manual.

9.3 Serum and Plasma Marker Studies

Sera will be collected prior to dosing on Day 1 of Cycles 1-6, and the EOC/EOT evaluation. Plasma will be collected prior to dosing on Day 1 of Cycle 1, Cycles 3-6, and the EOC/EOT evaluation. Additionally, subjects will have whole blood for serum drawn 20-26 hours post-CRS-207 infusion of Cycles 3-6. Subjects receiving additional treatment courses will only have whole blood for serum and plasma drawn during Cycle 4 and Cycle 6. The humoral immune responses directed against *Lm* and mesothelin will be evaluated by using enzyme-linked immunosorbent assay (ELISA) for *Lm*- and mesothelin-specific antibodies. In addition, potential therapeutic targets, biomarkers, and predictors of response and autoimmune toxicity will be evaluated. Sera and plasma are isolated and stored frozen (-80^{o}C) until use. Detailed instructions for processing and storage are provided in the Laboratory Manual.

9.4 Stool Samples Studies

Stool samples for microbial biomarker analyses will be collected prior to dosing on Day 1 of Cycle 1, and prior to Day 8 or Day 9 (for Arms B and A respectively) of Cycle 4 when available. The Cycle 4 sample may be collected at any time from Day 1 to Day 8 or 9. Stool samples will only be collected during the first course.

Microbial DNA will be isolated from stool samples and prepared for 16S V4 sequencing to profile microbial species represented in the gut pre- and post-treatment. In addition, microbial DNA will be subjected to whole genome metagenomics profiling of microbial species via shotgun sequencing for detailed functional and pathway analysis to determine the change in the species and functions in response to treatment. Further bioinformatics analyses will be performed with these sequencing data to identify candidate microbial biomarkers, and predictors of response. Detailed instructions for stool collection, shipment, and storage are provided in the Laboratory Manual.

9.5 Diagnostic Tissue Samples

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

10. STUDY CALENDAR

Subjects on both arms will receive treatment every 3 weeks for 6 cycles of treatment within a course. A course of treatment will be 20 weeks, with 16 weeks of treatment followed by an end-of-course (EOC) or end-of-treatment (EOT) evaluation approximately 4 weeks after the last study treatment administration in the course.

10.1 Treatment Arm A

Study Procedures	Pre-Study	Random-ization (R)	Cycle 1[25]			Cycle 2			Cycle 3					Cycle 4					Cycle 5					Cycle 6					EOC/ EOT[26]
			D1	D2	D4[24]	D1	D2	D4[24]	D1	D2	D3	D5[24]	D9	D1	D2	D3	D5[24]	D9	D1	D2	D3	D5[24]	D9	D1	D2	D3	D5[24]	D9	
Visit Windows (days)[1]	-21 to D1	D-7 to D1	-	-	±1	- 2	-	±1	- 2	-	-	±1	+1	- 2	-	-	±1	+1	- 2	-	-	±1	+1	- 2	-	-	±1	+1	+/- 7
CY			X			X																						
GVAX Pancreas Vaccine				X			X																					
CRS-207										X					X					X					X			
Nivolumab[2]			X			X			X					X					X					X				
Informed consent	X																											
Inclusion/exclusion criteria	X																											
Randomization (R)		X																										
Demographics	X																											
Medical, Cancer, & Con Med History[3]	X																											
Con Meds, Adverse Events			X	X	X	X	X	X	X	X	X	X		X	X	X	X		X	X	X	X		X	X	X	X		X
Physical Exam, ECOG PS[4]	X		X			X			X					X					X					X					X
Vitals, Weight, & Height[5]	X		X	X		X	X		X	X				X	X				X	X				X	X				X
Hematology, Chemistry[6, 12]	X		X			X			X		X		X	X		X		X	X		X		X	X		X		X
Endocrine[7, 12]			X			X			X					X					X					X					X

Study Procedures	Pre-Study	Random-ization (R)	Cycle 1[25]			Cycle 2			Cycle 3					Cycle 4					Cycle 5					Cycle 6					EOC/ EOT[26]
			D1	D2	D4[24]	D1	D2	D4[24]	D1	D2	D3	D5[24]	D9	D1	D2	D3	D5[24]	D9	D1	D2	D3	D5[24]	D9	D1	D2	D3	D5[24]	D9	
Urinalysis[8, 12]	X		X			X			X					X					X					X					X
CD4 count, virology[9]	X																												
Coagulation panel[10]	X																												
Pregnancy Test[11]	X					**X**			**X**					**X**					**X**					**X**					
CA19-9 [12]	X		X			X			X					X					X					X					X
ECG[13]	X																												X
CT/MRI, RECIST/irRC[14]	X													X															X
Vaccine Site Reactions[15]					X			X																					
Whole blood for PBMC and plasma[16]			X						X				X	X				X	X					X					X
Serum[16]			X			X			X		X			X		X			X		X			X		X			X
Stool Samples[17]			X											X															
HLA[18]			X																										
Lactoferrin[19]			X																										
Archival Tissue[20]	X																												
Tumor Biopsies[21]		X												X															
Antibiotics[22]																												X	X
Blood sample for CRS-207 testing[23]																													X

1: If necessary, a scheduled cycle may be delayed for up to 1 week. Longer delays to be approved by the IND Sponsor, Medical Monitor and/or Protocol Chair.
2: Nivolumab will be administered to subjects randomized to Arm A only Subjects on Arm A should be observed for a minimum of 30 minutes between CY and nivolumab administrations.
3: Cancer history includes: primary site of cancer, gross location of primary tumor, secondary sites of cancer, histology, histologic grade, date of initial diagnosis, date of metastatic diagnosis, prior cancer therapy regimens.
4: Complete physical examination and assessment of ECOG PS will be completed at baseline; focused physical examinations and assessment of ECOG PS will be conducted thereafter. Day 1 Physical examination and ECOG status may be done up to 1 day prior to dosing.
5: Blood pressure, pulse, respiratory rate, and temperature are required as indicated. Weight and pulse oximetry will be obtained at baseline and prior to each cycle. Height will be taken at or prior to screening only. Vitals should be collected prior to CY administration and prior to and after GVAX pancreas vaccine administration. Nivolumab: vitals will be collected prior to, every 30 minutes during (± 15 minutes), and at the end of infusion (± 15 minutes). CRS-207: vital signs will be obtained every 30 minutes (± 15 minutes) during infusion and every hour (± 15 minutes) during post-infusion follow-up. Subjects will be observed for at least 4 hours after each CRS-207 infusion. Subjects who are not stable enough to be released at 4 hours after infusion should continue to be monitored until stable. Presence of fever alone does not indicate subject is not clinically stable.
6: Clinical hematology: CBC with differential ANC, ALC, AEC, and platelet count; serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, LDH, ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin, amylase, total protein, albumin, calcium, magnesium, and phosphate. Required labs on Day 2 only after CRS-207 dosing: Any unexpected Grade 3 or greater laboratory abnormalities should be repeated within 24-72 hours.
7: TSH (Total T3 and free T4 if TSH abnormal).
8: Bilirubin, blood, glucose, ketones, leukocytes, nitrite, pH, color, protein, RBC and WBC count, and specific gravity.
9: Virology screen: HIV antibody, hepatitis B surface antigen and hepatitis C antibody; additional virology may also be evaluated. Subjects who are hepatitis C antibody positive and confirmed negative viral load at screening will be allowed to enroll.
10: Coagulation panel: D-dimer, fibrinogen, international normalized ratio of prothrombin time, APTT
11: Pregnancy tests will be administered to WOCBP: serum pregnancy test is required at screening; urine pregnancy tests are required before doses on Day 1 of dosing weeks.
12: Labs may be collected within a window of up to 3 days prior to dosing. Blood draws must not be collected from a central line for at least 4 days after infusion of CRS-207.
13: ECG should be performed at baseline and at the EOT visit.
14: Spiral CT of thorax, abdomen and pelvis (and other imaging studies as clinically indicated to evaluate suspected sites of metastatic disease). If a subject cannot have a CT scan (e.g., allergy to contrast dye), an MRI should be performed. On study radiologic evaluations and tumor measurements (RECIST and irRC per **Appendix C** and **Appendix D**) will be performed every 10 weeks (± 1 week; starting from the date of first treatment) including the EOT evaluation (± 4 weeks). If the EOT visit occurs early, scans do not need to be repeated if one has been done within the past 6 weeks. Weeks are in reference to calendar week and should not be adjusted due to dosing delays.
15: Injection-site reactions will be evaluated on Day 4 after GVAX pancreas vaccinations
16: Up to 200 mL of whole blood may be drawn up to 72 hours prior to dosing and must be processed by sponsor-qualified operators within 6 hours of collection and stored in liquid nitrogen. During Cycles 3 and 4 of the first course, an additional blood draw for PBMC/plasma will be taken on Day 9,

therefore the volume drawn may be split between Day 1 and Day 9 (e.g., 100 mL per timepoint). Approximately 10 mL of blood for serum for immune monitoring will be drawn as indicated. Day 3 blood draws (after CRS-207 only) should be taken between 20 and 26 hours after start of dosing. Subjects receiving additional treatment courses will only have whole blood for isolation of PBMCs, plasma, and serum drawn during Cycle 4 and Cycle 6.

17: Stool samples for microbial biomarker analyses will be collected during Course 1 when available. Stool samples for Cycle 4 may be collected any time from Day 1 to Day 9 when available. Detailed instructions for stool collection and shipment are provided in the Laboratory Manual.

18: HLA-typing to include HLA class I type A and B, low resolution. HLA typing is only done during the first course of study treatment.

19: Lactoferrin values at baseline (Cycle 1, Day 1, prior to dosing) and when a subject is being evaluated for potential colitis will be collected when available.

20: Attempts to obtain surgical or biopsy archival tumor samples will be made for every subject until the sample is obtained or documentation that the sample cannot be obtained. The tissue sample should have proper size to enable IHC analysis of PD-L1. Detailed instructions for tissue collection, processing and shipment are provided in the Laboratory Manual.

21: Tumor biopsies to be taken (if a subject's tumor is thought to be reasonably safe and easy to biopsy) at baseline and at Cycle 4 (4-6 cores per timepoint). The Cycle 4 biopsy has a ± 1 week window. Additional optional biopsies may be obtained later in the course of study treatment. The tissue sample should have proper size to enable IHC analysis of PD-L1. Fine needle aspiration will not be acceptable. Detailed instructions for tissue collection, processing and shipment are provided in the Laboratory Manual. Biopsies will only be collected during the first course of study treatment

22: [redacted]

23: [redacted]

24: Day 4 and 5 (± 1 day) assessments may be conducted by telephone or email.

25: Cycle 1 Day 1 evaluations do not need to be repeated if they were conducted within 3 days of the pre-study evaluations.26: Subjects will return to the study site at EOC for continuation of treatment or an EOT evaluation. EOT follow-up will occur 28 (±7) days after the final dose. NOTE: CT scan assessment at EOT will occur 28 days (± 4 weeks) after the final dose. If the EOT visit occurs early, an assessment for AEs should be made by telephone or email on day 28 (±1) after last study dose. Subjects who discontinue from treatment should be contacted every three months (+/- 2 weeks) to monitor overall survival. Information of other cancer therapies after discontinuation from the study treatment will be collected as well. Subjects who discontinue treatment from Arm A should be contacted by telephone or email at 100 days (+ 14 day reporting window) to assess for SAEs that occur in the follow-up period.

10.2 Treatment Arm B

Study Procedures	Pre-Study	Random-ization (R)	Cycle 1[23]			Cycle 2			Cycle 3				Cycle 4				Cycle 5				Cycle 6				EOC/ EOT[24]
			D1	D2	D4[22]	D1	D2	D4[22]	D1	D2	D4[22]	D8	D1	D2	D4[22]	D8	D1	D2	D4[22]	D8	D1	D2	D4[22]	D8	
Visit Windows (days)[1]	-21 to D1	D-7 to D1	-	-	±1	- 2	-	±1	- 2	-	±1	+1	- 2	-	±1	+1	- 2	-	±1	+1	- 2	-	±1	+1	+/- 7
CY			X			X																			
GVAX Pancreas Vaccine				X			X																		
CRS-207									X				X				X				X				
Informed consent	X																								
Inclusion/exclusion criteria	X																								
Randomization (R)		X																							
Demographics	X																								
Medical, Cancer, & Con Med History[2]	X																								
Con Meds, Adverse Events			X	X	X	X	X	X	X	X	X		X	X	X		X	X	X		X	X	X		X
Physical Exam, ECOG PS[3]	X		X			X			X				X				X				X				X
Vitals, Weight, & Height[4]	X		X	X		X	X		X				X				X				X				X
Hematology, Chemistry[5, 10]	X		X			X			X	X		X	X	X		X	X	X		X	X	X		X	X
Urinalysis[6, 12]	X																								X
CD4 count, virology[7]	X																								
Coagulation panel[8]	X																								
Pregnancy Test[9]	X					**X**			**X**				**X**				**X**				**X**				
CA19-9 [10]	X		X			X			X				X				X				X				X
ECG[11]	X																								X
CT/MRI, RECIST/irRC[12]	X												X												X

Study Procedures	Pre-Study	Random-ization (R)	Cycle 1[23]			Cycle 2			Cycle 3				Cycle 4				Cycle 5				Cycle 6				EOC/ EOT[24]
			D1	D2	D4[22]	D1	D2	D4[22]	D1	D2	D4[22]	D8	D1	D2	D4[22]	D8	D1	D2	D4[22]	D8	D1	D2	D4[22]	D8	
Vaccine Site Reactions[13]					X			X																	
Whole blood for PBMC and plasma[14]			X						X			X	X			X	X				X				X
Serum[14]			X			X			X	X			X	X			X	X			X	X			X
Stool Samples[15]			X										X												
HLA[16]			X																						
Lactoferrin[17]			X																						
Archival Tissue[18]	X																								
Tumor Biopsies[19]		X											X												
Antibiotics[20]																								X	X
Blood sample for CRS-207 testing[21]																									X

1: If necessary, a scheduled cycle may be delayed for up to 1 week. Longer delays to be approved by the IND Sponsor, Medical Monitor and/or Protocol Chair.

2: Cancer history includes: primary site of cancer, gross location of primary tumor, secondary sites of cancer, histology, histologic grade, date of initial diagnosis, date of metastatic diagnosis, prior cancer therapy regimens.

3: Complete physical examination and assessment of ECOG PS will be completed at baseline; focused physical examinations and assessment of ECOG PS will be conducted thereafter. Day 1 Physical examination and ECOG status may be done up to 1 day prior to dosing.

4: Blood pressure, pulse, respiratory rate, and temperature are required as indicated. Weight and pulse oximetry will be obtained at baseline and prior to each cycle. Height will be taken at or prior to screening only. Vitals should be collected prior to CY administration and prior to and after GVAX pancreas vaccine administration. Vital signs will be obtained every 30 minutes (± 15 minutes) during CRS-207 infusion and every hour (± 15 minutes) during post-infusion follow-up. Subjects will be observed for at least 4 hours after each infusion. Subjects who are not stable enough to be released at 4 hours after infusion should continue to be monitored until stable. Presence of fever alone does not indicate subject is not clinically stable.

5: Clinical hematology: CBC with differential ANC, ALC, AEC, and platelet count; serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, LDH, ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin, amylase, total protein, albumin, calcium, magnesium, and

phosphate. Required labs on Day 2 only after CRS-207 dosing: Any unexpected Grade 3 or greater laboratory abnormalities should be repeated within 24-72 hours.

6: Bilirubin, blood, glucose, ketones, leukocytes, nitrite, pH, color, protein, RBC and WBC count, and specific gravity.

7: Virology screen: HIV antibody, hepatitis B surface antigen and hepatitis C antibody; additional virology may also be evaluated. Subjects who are hepatitis C antibody positive and confirmed negative viral load at screening will be allowed to enroll

8: Coagulation panel: D-dimer, fibrinogen, international normalized ratio of prothrombin time, APTT

9: Pregnancy tests will be administered to WOCBP: serum pregnancy test is required at screening; urine pregnancy tests are required before doses on Day 1 of dosing weeks.

10: Labs may be collected within a window of up to 3 days prior to dosing. Blood draws must not be collected from a central line for at least 4 days after infusion of CRS-207. Any unexpected Grade 3 or greater laboratory abnormalities should be repeated within 24-72 hours.

11: ECG should be performed at baseline and at the EOT visit.

12: Spiral CT of thorax, abdomen and pelvis (and other imaging studies as clinically indicated to evaluate suspected sites of metastatic disease). If a subject cannot have a CT scan (e.g., allergy to contrast dye), an MRI should be performed. On study radiologic evaluations and tumor measurements (RECIST and irRC per **Appendix C** and **Appendix D**) will be performed every 10 weeks (+/- 1 week; starting from the date of first treatment) including the EOT evaluation (+/- 4 weeks). If the EOT visit occurs early, scans do not need to be repeated if one has not been done within the past 6 weeks. Weeks are in reference to calendar week and should not be adjusted due to dosing delays.

13: Injection-site reactions will be evaluated on Day 4 after GVAX pancreas vaccinations

14: Up to 200 mL of whole blood may be drawn up to 72 hours prior to dosing and must be processed by sponsor-qualified operators within 6 hours of collection and stored in liquid nitrogen. During Cycles 3 and 4 of the first course only, an additional blood draw for PBMC/plasma will be taken on Day 8, therefore the volume drawn may be split between Day 1 and Day 8 (e.g., 100 mL per timepoint). Approximately 10 mL of blood for serum for immune monitoring will be drawn as indicated. Day 2 blood draws (after CRS-207 only) should be taken between 20 and 26 hours after start of dosing. Subjects receiving additional treatment courses will only have whole blood for isolation of PBMCs, plasma, and serum drawn during Cycle 4 and Cycle 6.

15: Stool samples for microbial biomarker analyses will be collected during Course 1 when available. Stool samples for Cycle 4 may be collected any time from Day 1 to Day 8 when available. Detailed instructions for stool collection and shipment are provided in the Laboratory Manual.

16: HLA-typing to include HLA class I type A and B, low resolution. HLA typing is only done during the first course of study treatment

17: Lactoferrin values at baseline (Cycle 1, Day 1, prior to dosing) and when a subject is being evaluated for potential colitis will be collected when available.

18: Attempts to obtain surgical or biopsy archival tumor samples will be made for every subject until the sample is obtained or documentation that the sample cannot be obtained. The tissue sample should have proper size to enable IHC analysis of PD-L1. Detailed instructions for tissue collection, processing and shipment are provided in the Laboratory Manual.

19: Tumor biopsies to be taken (if a subject's tumor is thought to be reasonably safe and easy to biopsy) at baseline and at Cycle 4 (4-6 cores per timepoint). The cycle 4 biopsy has a ± 1 week window. Additional optional biopsies may be obtained later in the course of study treatment. The tissue sample should have proper size to enable IHC analysis of PD-L1. Fine needle aspiration will not be acceptable. Detailed instructions for tissue collection, processing and shipment are provided in the Laboratory Manual. Biopsies will only be collected during the first course of study treatment

20: [redacted]

21: [redacted]

22: Day 4 (± 1 day) assessments may be conducted by telephone or email.

23: Cycle 1 Day 1 evaluations do not need to be repeated if they were conducted within 3 days of the pre-study evaluations.

24: Subjects will return to the study site at EOC for continuation of treatment or an EOT evaluation. EOT follow-up will occur 28 (±7) days after the final dose. NOTE: CT scan assessment at EOT will occur 28 days (± 4 weeks) after the final dose. If the EOT visit occurs early, an assessment for AEs should be made by telephone or email on day 28 (±1) after last study dose. Subjects who discontinue from treatment should be contacted every three months (± 2 weeks) to monitor overall survival. Information of other cancer therapies after discontinuation from the study treatment will be collected as well.

11. STUDY ENDPOINTS

11.1 Primary Endpoint

The primary endpoint is OS, measured from date of randomization until death or end of follow-up (OS will be censored on the date the subject was last known to be alive for subjects without documentation of death at the time of analysis).

11.2 Secondary Endpoints

The secondary endpoints are as follows:

- Objective disease responses, duration of response, PFS measured by RECIST, immune-related progression-free survival (irPFS), and time to progression (TTP)
  - Progression-free survival (PFS) is defined as the number of months from the date of randomization to disease progression (PD or relapse from CR as assessed using RECIST 1.1 criteria) or death due to any cause.
  - Immune-related progression-free survival (irPFS) is defined as the number of months from the date of randomization to disease progression (PD or relapse from CR as assessed using irRC RECIST 1.1 criteria) or death due to any cause.
  - Time to-progression (TTP) is defined as the number of months from the date of randomization to the date of documented disease progression (PD or relapse from CR as assessed using RECIST 1.1 criteria).
- Tumor marker kinetics measured by change in serum CA19-9 concentrations from baseline
- Safety assessed by the following measures:
  - AEs
  - Injection-site reactions (after GVAX pancreas vaccine injections only)
  - Nivolumab-related infusion reactions
  - CRS-207-related infusion reactions
  - Immune-related AEs
  - Unacceptable toxicities
  - Vital signs: BP, pulse, respiratory rate, temperature
  - Physical examination
  - Changes in ECG readings
  - Clinical hematology: complete blood count (CBC) with differential ANC, ALC, AEC, and platelet count
  - Clinical serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (BUN), creatinine, lactate dehydrogenase (LDH), ALT, AST, alkaline phosphatase, amylase, bilirubin (total), total protein, albumin, calcium, magnesium and phosphate

11.3 Exploratory Endpoints

Exploratory endpoints are as follows:

- Objective disease responses and duration of response measured by irRC
- Humoral and cellular immune responses directed against *Lm* and mesothelin assessed by using the following measures:

  - ELISPOT or intracellular cytokine staining assays of PBMC
  - Induction of proinflammatory cytokines and chemokines in the serum
  - ELISA detection of mesothelin- and *Lm*-specific antibodies in the serum
- Immune subset analyses by IHC and gene expression profiling of tumor tissue
- Immune subset analyses in PBMCs including effector, helper, and regulatory T cells, NK cells, and macrophages
- Telomere length of lymphocytes
- Thyroglobulin and galectin-3 antibody responses
- Microbial community analysis and whole metagenome functional profiling analysis of stool samples

12. DATA REPORTING / REGULATORY REQUIREMENTS

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

12.1 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 paper or 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.

If electronic CRFs are used, training will be provided for the EDC system. All personnel using the EDC system must have appropriate education, training and experience. The investigator will be provided with EDC User's Guide (contained in the Study Reference Manual [SRM]) on the use of the EDC system. The investigator will be responsible for documenting employee education, training and previous experience that pertains to the EDC system.

The investigator must maintain adequate security of the EDC system, including documentation that all users have been trained on the appropriate SOPs and a list of authorized users. To ensure attributability, all personnel responsible for data entry must obtain a unique electronic signature before any data can be entered in the CRFs. The system must be configured to ensure that the signer cannot readily repudiate the signed record as not genuine. Authorized study personnel will be assigned a unique password and associated electronic signature after receiving SOP training.

If EDC systems other than those provided and maintained by the IND Sponsor or designee are used for documentation and data capture, the investigator must ensure that the systems are validated and ensure data backup as described in **Section 12.4**.

<u>Protocol Chair</u>
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.

12.2 Independent Data Monitoring Committee (DMC)

A DMC will monitor the study for safety, efficacy in the context of subject risk/benefit, and perform other functions according to a charter that defines its roles and responsibilities. The DMC for this clinical study contains three medical oncologists from other disciplines and a statistician who are not affiliated with this clinical trial protocol. The DMC will review safety data after approximately 25%, 50%, 75% and 100% of total planned subjects have been randomized and treated and 6 months after the last subject is randomized, but not more frequent than every 4 months. Additionally, one pre-planned formal interim analysis to review and assess efficacy in the context of risk/benefit will be conducted when approximately 50% of the expected events occur. A meeting of the DMC will also be convened if the safety stopping guidelines (**Section 5.8**) are triggered. Meetings will be convened by conference call or in person. The DMC will provide a written summary of their recommendations after each data review meeting. Further details describing the communication, dissemination and actions of DMC recommendations as well as committee procedures and policies, including table displays, will be described in the DMC charter.

12.2.1 Safety Review

At each scheduled meeting, the DMC will be provided with tables and/or listings summarizing all AEs, laboratory toxicities, discontinuations and subject deaths by treatment arm. The DMC may also request additional data or analyses. Since these are safety evaluations with no intent of stopping for positive efficacy, there will be no adjustments to the overall alpha level of the efficacy analysis from these safety reviews.

12.2.2 Interim Analysis

At the interim analysis, the DMC will be provided with outputs summarizing overall survival and tumor response data by treatment arm, as well as the outputs produced for Safety Reviews (Section 12.2.1). While there is no intent to stop early based on these results, adjustments to preserve the overall alpha level have been made to account for this interim analysis (Section 13.1).

12.3 Populations of Interest

The Full Analysis Set (FAS) includes all randomized subjects who received at least one dose of study treatment. FAS analyses will be conducted on the basis of the randomized treatment. All efficacy outcomes will be assessed using the FAS as the primary population for analysis.

The Intent to Treat (ITT) analysis set includes all randomized subjects, regardless of the amount or type of treatment received. It is distinguished from the FAS in that individuals who do not receive any doses of study treatment will be included. ITT analyses will be conducted on the basis of the randomized treatment. This population will be used for sensitivity analyses of OS and other selected efficacy endpoints.

The safety population includes all randomized subjects who received at least one dose of study treatment. The safety population will be conducted on the basis of the actual treatment received. All safety outcomes will be assessed using the safety population for analysis.

A Per-Protocol (PP) subset may also be used to analyze select efficacy endpoints and will be based on study treatment exposure (compliance and/or time on study treatment) and major protocol deviations. The criteria for inclusion in the PP subset will be finalized and documented prior to database lock.

12.4 Study Documentation

12.4.1 Informed Consent and Authorization for use and Disclosure of Protected Health Information

Written informed consent and authorization of use and disclosure of protected health information (PHI) must be obtained from each subject (or the subject's legally authorized representative) before performing any study-specific screening/baseline period

evaluations. One copy of the signed informed consent form (ICF) and authorization for use and disclosure of the PHI form will be given to the subject and the investigator will retain the original. The ICF and authorization for use and disclosure of PHI, which is prepared by the investigator or the site, must be reviewed and approved by the IND Sponsor, the study monitor (if applicable) and the site's IRB before the initiation of the study. The ICF must contain the 20 elements of informed consent described in ICH E6, Section 4.8. The authorization for use and disclosure of PHI must contain the elements required by Title 45 of the Code of Federal Regulations (CFR), Section 164.508(b), for valid authorizations.

12.4.2 Investigator Study Files

Documentation about the investigator and study staff, the IRB and the institution, is required before study site initiation. A list of required documents will be provided by the IND Sponsor or designee to each participating investigator. Copies of these documents as well as supplemental information, such as the investigator's obligations, IB, clinical study protocol and amendments, safety information, investigational agent information, biological samples and laboratory procedures, SRM, study logs and IND Sponsor/investigator/study monitor correspondence will be kept on-site in study site-specific binders.

The IND Sponsor or designee will be responsible for maintaining original and backup of all CRF data. The investigator is responsible for maintaining backup of all electronic data systems used for primary documentation or source documentation. Backup of electronic data will be performed periodically as described in the site-specific SOPs. Backup records must be stored at a secure location on site and backup and recovery logs must be maintained to facilitate data recovery. If an electronic medical records system that is not supported by the IND Sponsor or designee (or is discontinued or decommissioned) is used, the investigator must maintain a system to retrieve these records or arrange for the transfer of these records to an alternate electronic format or to paper.

Changes to any electronic records require an audit trail, in accordance with 21 CFR 11.10(e), and should include who made the changes and when and why the changes were made. An audit trail is defined as a secure, computer-generated, time-stamped electronic record that will allow reconstruction of the course of events relating to the creation, modification and deletion of an electronic record. Audit trails must be created incrementally, in chronological order and in a manner that does not allow new audit trail information to overwrite existing data. Audit trails should be in a readable format and readily available at the study site and any other location where electronic study records are maintained.

Audit trails are generated automatically for eCRFs. The investigator is responsible for maintaining audit trails of all electronic data systems used for primary documentation or source documentation.

12.4.3 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.

12.4.4 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.

12.4.5 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, Aduro, 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.

12.5 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.

12.6 Study Monitor Function and Responsibility

The study monitor, in accordance with the IND Sponsor (or designee) requirements, will ensure that the study is conducted and documented properly by carrying out the relevant activities outlined in ICH E6, Sections 5.18.4, 5.18.5 and 5.18.6.

12.7 General Information

The investigator should refer to the IB, product labels, SRM, clinical protocol and appendices and other information provided during the study for further information about the investigational agents or details of the procedures to be followed during the course of this study.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

Sample size. The primary endpoint is OS, and will be calculated from date of randomization to death. For subjects without documentation of death at the time of analysis, OS will be censored on the date the subject was last known to be alive. The OS of subjects randomized to CY/nivolumab/GVAX pancreas vaccine followed by nivolumab/CRS-207 will be compared to subjects randomized to CY/GVAX pancreas vaccine followed by CRS-207.

Power is computed for a 2-stage group sequential design with a single interim analysis. To control the overall two-sided type I error rate of 0.15 for the primary endpoint of OS, an O'Brien Fleming-like spending function will be used to account for one interim analysis. The amount of alpha spent (two-sided) for the interim analysis is 0.02361. The interim analysis is performed when approximately 50% of the total number of events required for the final analysis have been observed (approximately 42 events). Accordingly, the p-value for the final analysis needs to be less than 0.14278 in order to reject the null hypothesis of equal survival.

Assuming a uniform accrual period of 18 months with a follow-up of 12 months, 102 subjects (51 per arm) will be treated to achieve 84 deaths in the CY/nivolumab/GVAX and CY/GVAX arms combined. At the time of final analysis, this will provide 80% power to detect an HR of 1.66, i.e. an increase in median OS from 6 to 9.96 months, with a 2-sided type 1 error rate of 0.14278. Based upon these calculations, we expect to observe 38 and 46 deaths over the course of the study in the CY/nivolumab/GVAX and CY/GVAX arms, respectively. No losses to

follow-up were included in these calculations. As noted in Section 12.3, the primary analysis will be performed using the FAS, which will consist of all randomized subjects who receive at least one dose of study treatment. As such, subjects will be enrolled until 102 subjects have received at least one dose of treatment (CY, nivolumab, GVAX, or CRS-207). Assuming that at most 5% of subjects do not receive study treatment, approximately 108 subjects will be enrolled.

Statistical Analyses

All statistical analyses will be performed using SAS® version 9 or higher.

Data will be summarized descriptively by treatment arm and overall. The descriptive summary for the categorical variables will include counts and percentages. The descriptive summary for the continuous variables will include means, medians, standard deviations and minimum and maximum values. The descriptive summary of time to event data will include median, 25th and 75th percentiles and standard error. All data will be listed for all subjects.

All statements of statistical significance will be based on a 2-tailed test with an overall 0.15 level of significance, unless stated otherwise. All confidence intervals will be 95%, unless stated otherwise. Time-to-event outcomes such as OS will be analyzed using Kaplan-Meier estimates, log-rank tests, and Cox proportional hazards models. Where applicable, comparisons between groups will be made using a Chi-square test or logistic regression for binary variables and analysis of variance (ANOVA) or analysis of covariance (ANCOVA) for continuous variables. Non-parametric alternatives (e.g. Fisher's exact test or Kruskal-Wallis tests) will be considered as needed.

For correlative studies, plots will be used to show the changes in immune response over time both for each individual and for each treatment group. For each treatment, comparisons in the pre and post-treatment responses will be compared using paired t-tests (or Wilcoxon signed rank tests if appropriate) for continuous variables and McNemar's tests for dichotomous or categorical variables. Associations between immune parameters will be explored graphically (e.g. scatterplots, boxplots) and numerically (e.g., correlations, Fisher's exact tests). Regression techniques will be used to explore the differences between the treatment arms for cross-sectional data (e.g., linear and logistic regression) and longitudinally with appropriate correction for correlation between repeated measurements (e.g., GEE and linear mixed effects models).

Demographics and baseline characteristics will be summarized by treatment arm. All differences will be interpreted for their clinical significance and potential use as covariates in sensitivity analyses of efficacy endpoints.

For the primary analysis of overall survival, subjects without documentation of death at the time of analysis will be censored as of the date the subject was last known to be alive. Kaplan-Meier methodology will be used to estimate the survival probabilities and median survival time for each treatment arm. Comparisons among treatment groups will use the stratified log-rank test, using disease status at study entry as the stratification factor, to compare OS. If proportional hazard assumptions are not violated, the hazard ratio will be estimated using the Cox regression model. If violated, treatment effect will be summarized by 1 or more appropriate summary statistics, such as hazard ratios from a piecewise proportional hazards model or other semi-nonparametric approach. Sensitivity analyses based upon the ITT and PP analysis sets will be

performed using the methods described above.

Additional details describing the handling the secondary and exploratory endpoints will be described in a separate statistical analysis plan (SAP).

The effects of discontinuation of nivolumab, noncompliance, time to first dose, treatment discontinuations, premature withdrawal from study and covariates will be assessed to determine the impact on the general applicability of results from this study. Details of the analysis, including the definitions of endpoints, methods for censoring, handling of missing data, transformations and other data handling procedures will also be provided in the SAP. Exploratory analyses of the data will be conducted as deemed appropriate.

The assumptions used in the sample size calculations may be assessed at the time of the interim analysis to determine if the planned duration of required follow up time and/or number of treated subjects is appropriate to reach the targeted number of deaths. The sample size, i.e, targeted number of deaths, will not be adjusted, nor will any by-treatment results be examined to assess the assumptions. As such, there will be no additional adjustments needed to the overall alpha level from this activity. Further details for the interim and final analysis will be described in a separate statistical analysis plan (SAP).

13.2 Safety Analysis

The safety analysis will be performed in all treated subjects. AE data will be listed individually and incidence of AEs summarized by system organ class and preferred terms within a system organ class for each treatment group. When calculating the incidence of AEs, each AE (based on preferred terminology defined by Medical Dictionary for Regulatory Activities (MedDRA; Version 13.1, or later) will be counted only once for a given subject. In analyses of grade and causality, if the same AE occurs on multiple occasions, the highest grade and strongest relationship to study drug will be assumed. If 2 or more AEs are reported as a unit, the individual terms will be reported as separate experiences. Vaccine-site reactions will be listed and tabulated separately from the AEs.

Changes in vital signs, hematology and clinical chemistry parameters from baseline to the end of the study will be examined. Toxicity will be tabulated by type and grade. Toxicities will be characterized according to the CTCAE version 4.03. Treatment-emergent changes from normal to abnormal values in key laboratory parameters will be identified.

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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

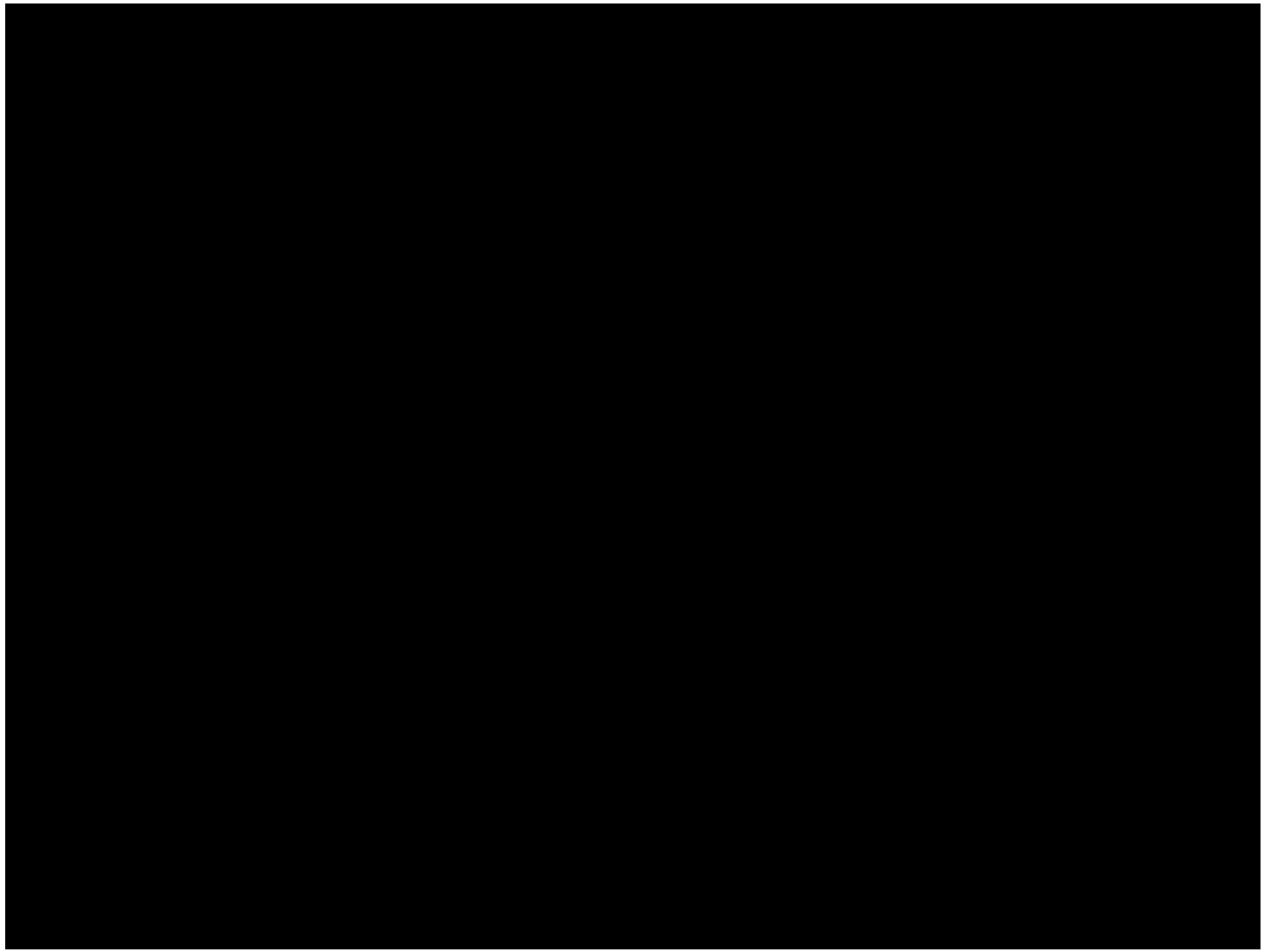
These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Protocol Chair and/or Medical Monitor representing the IND Sponsor. The guidance applies to all immuno-oncology (I-O) agents and regimens.

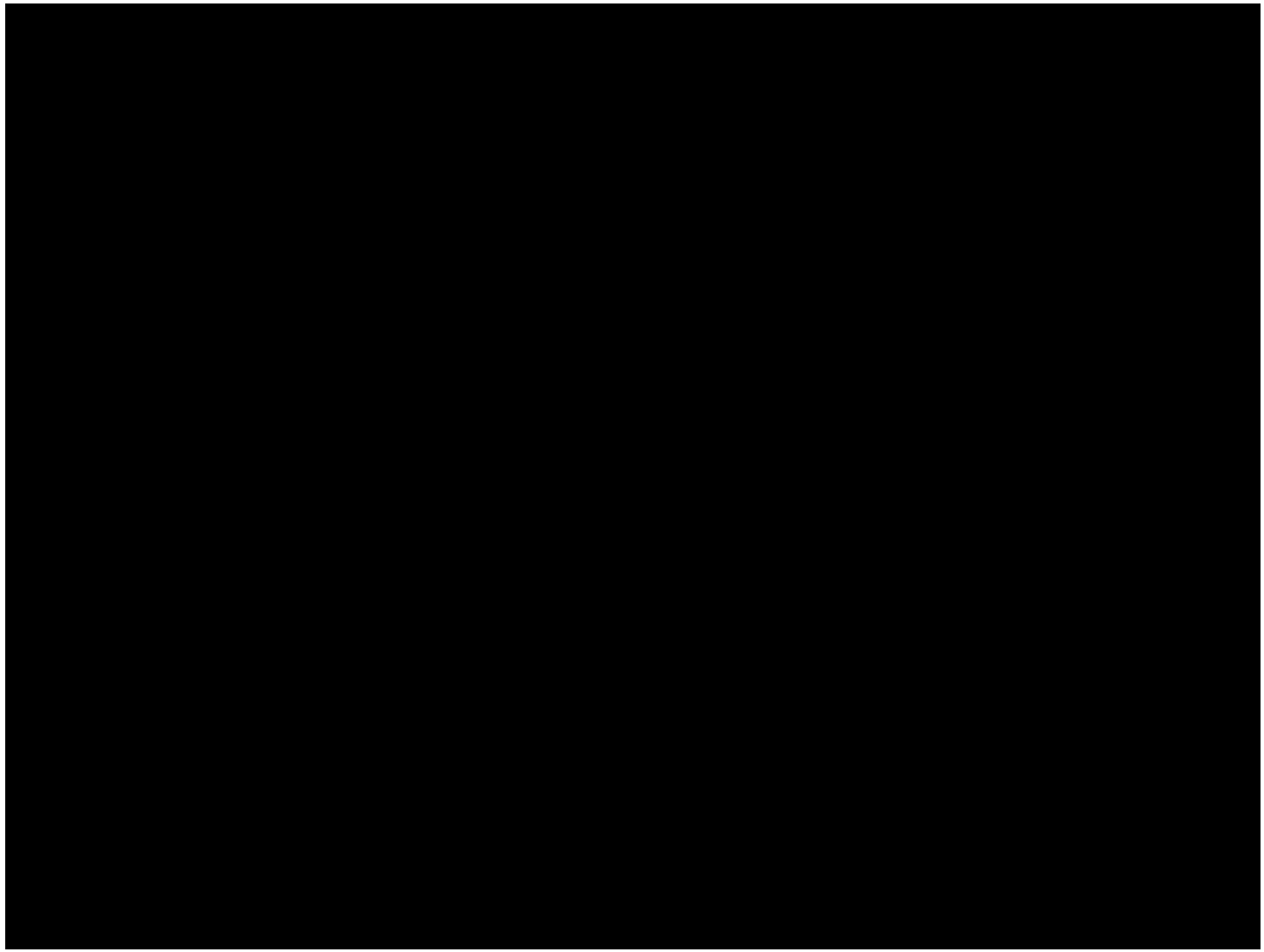
A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

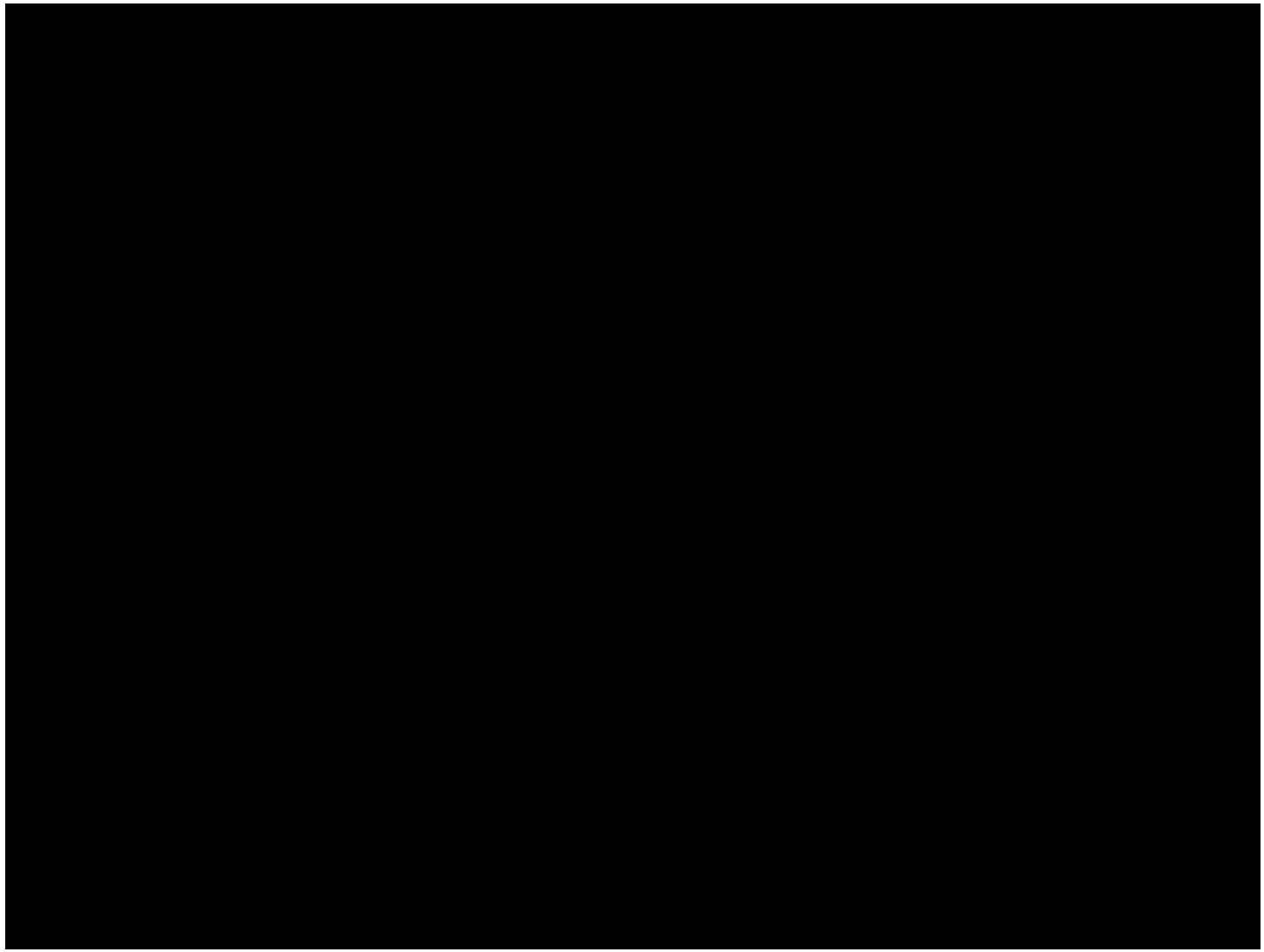
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory subjects with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

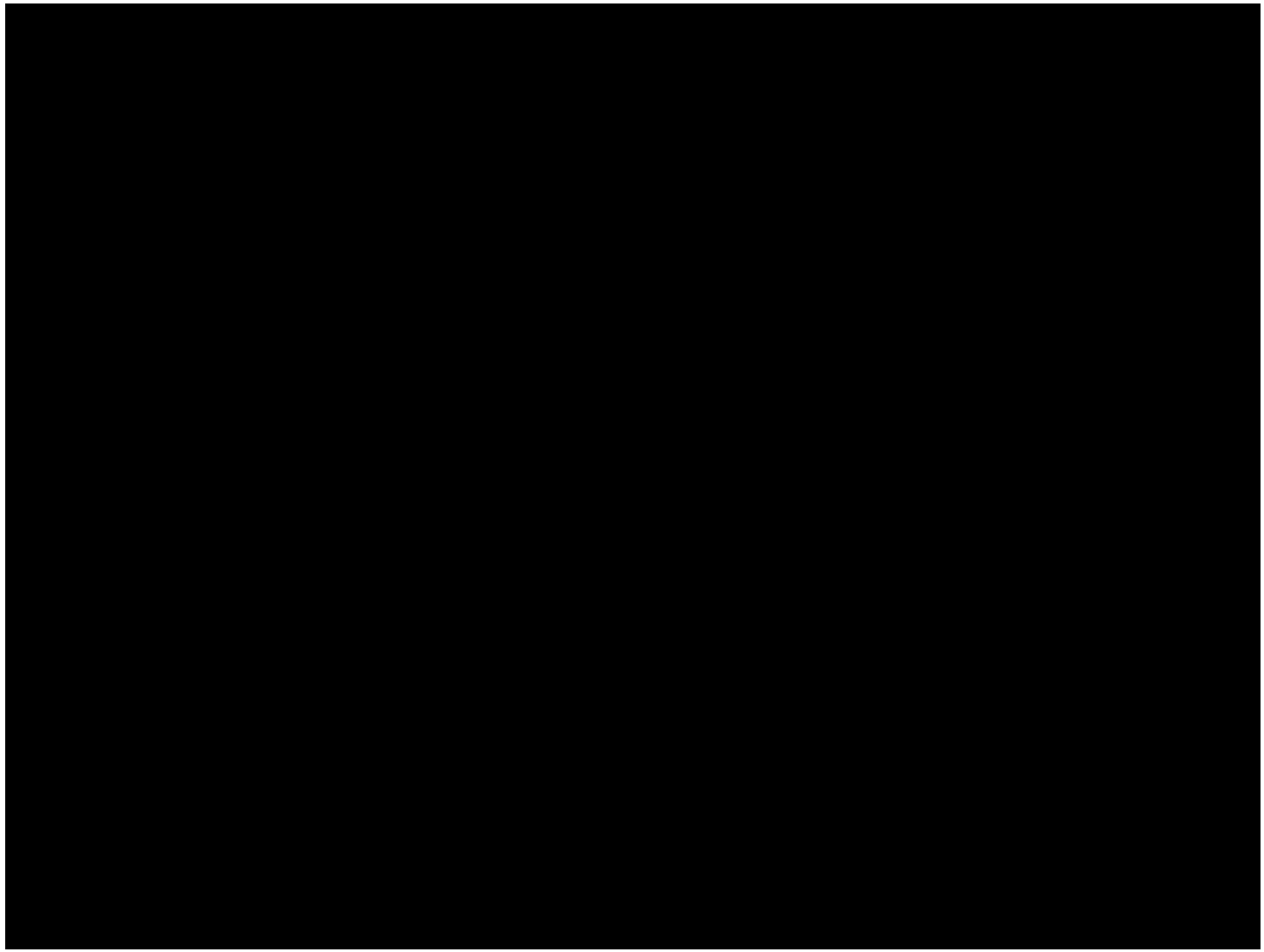
Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

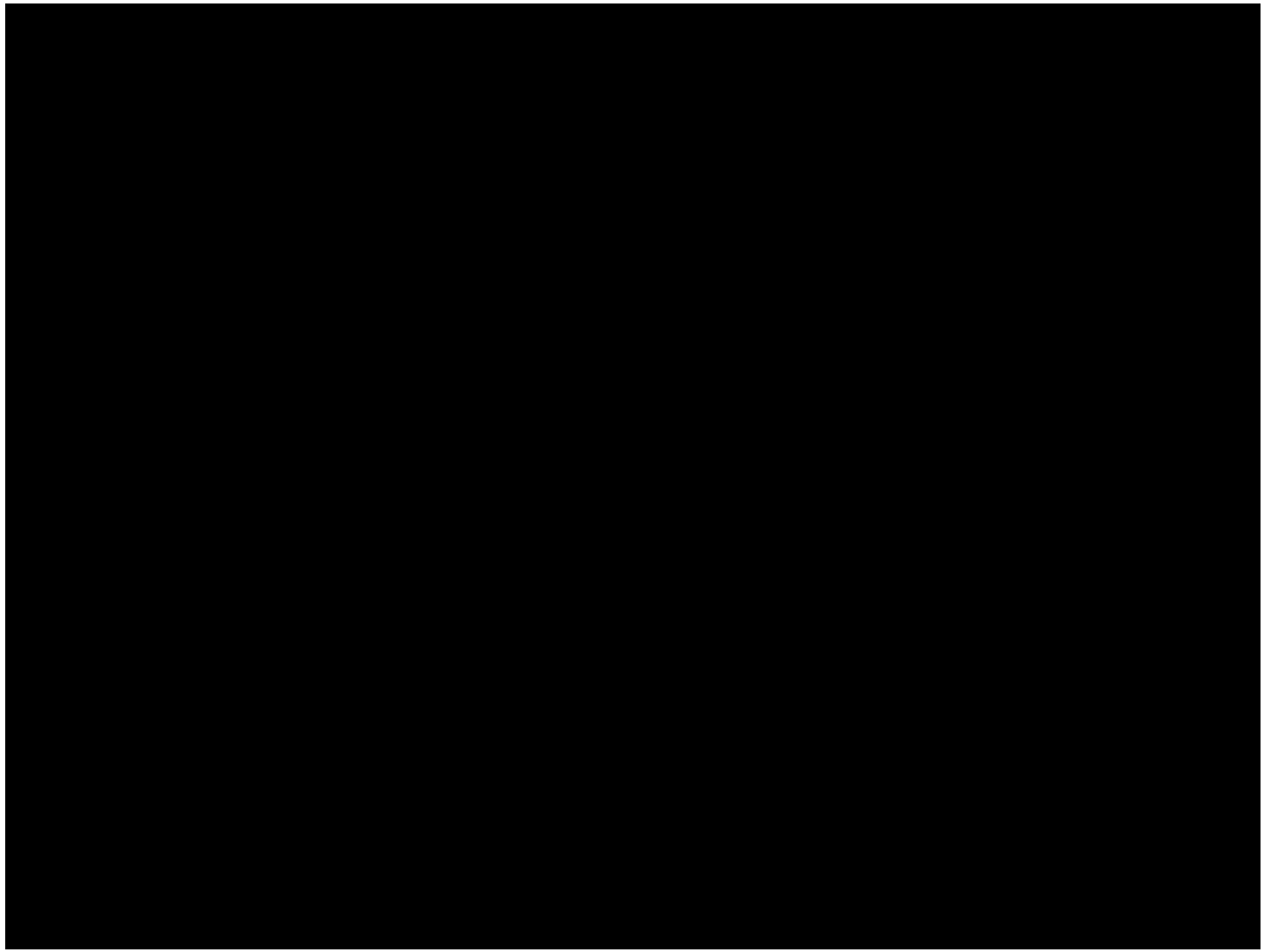
The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

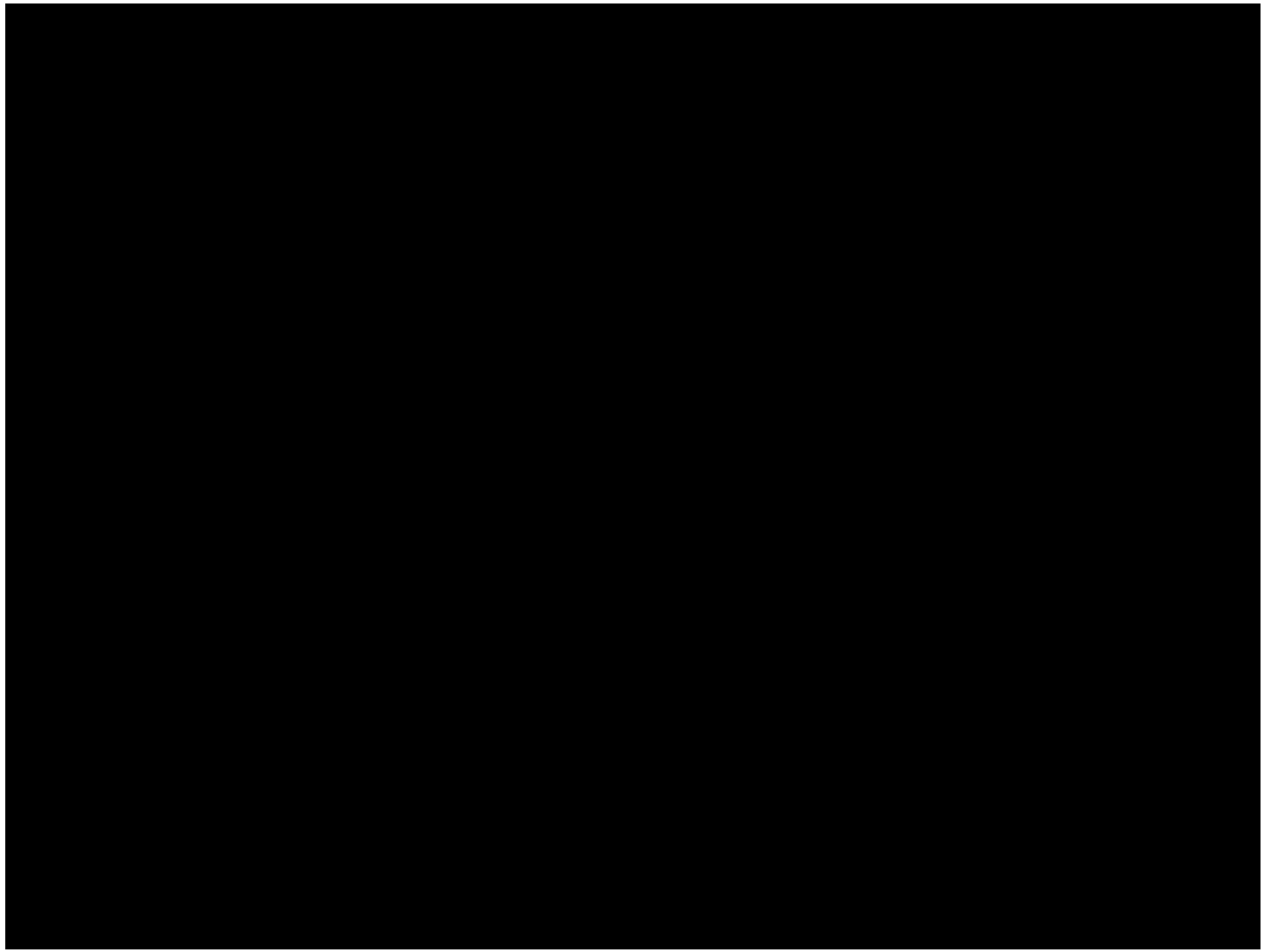


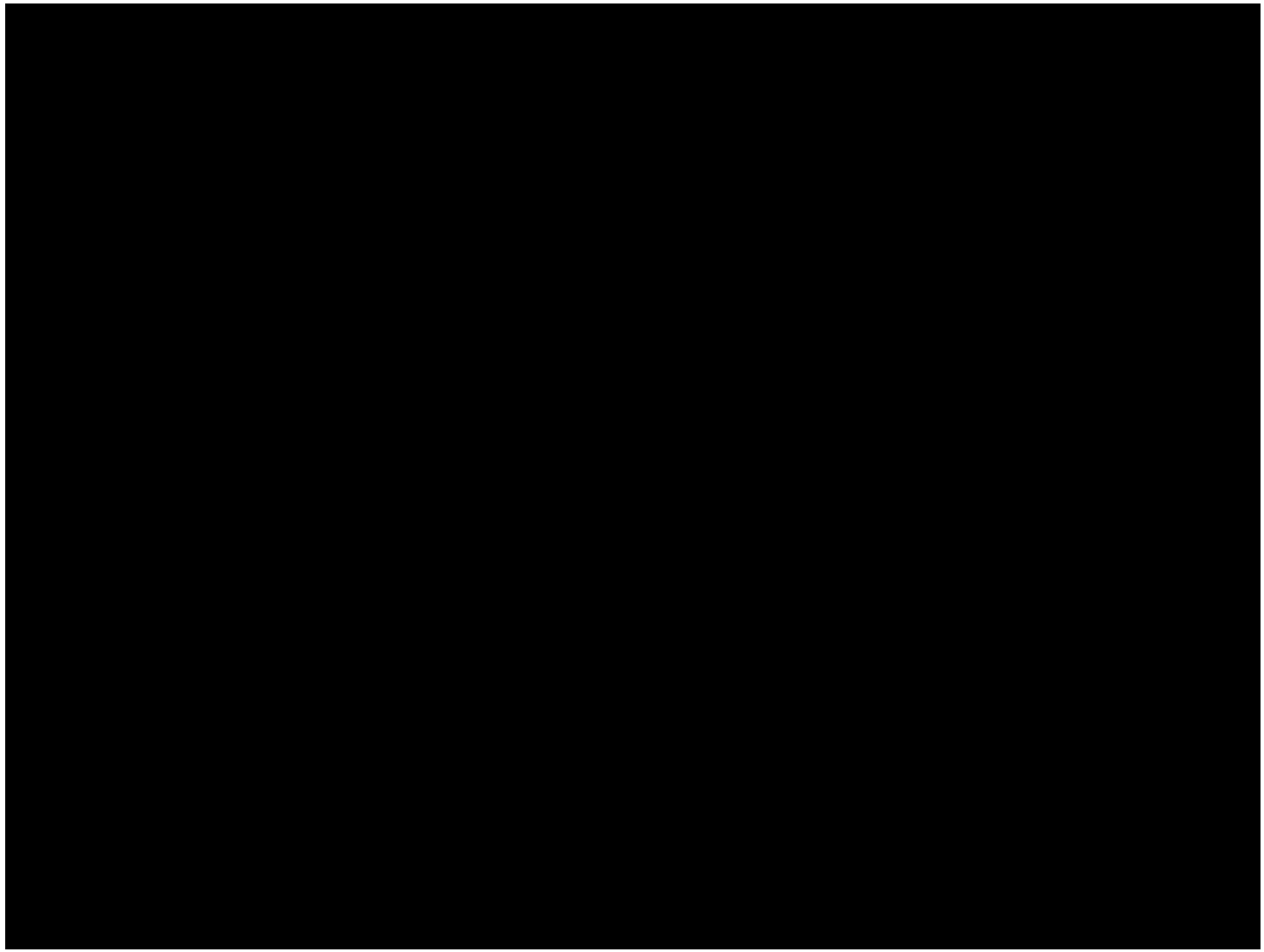












APPENDIX C: Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors

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 subject, 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 subject 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 subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Subjects 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: Subjects 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

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. 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.

APPENDIX D: Immune-Related Response Criteria

Comparison between RECIST 1.1 criteria and the irRC

	RECIST 1.1	irRC RECIST 1.1
New, measurable lesions (i.e., ≥ 5mm)	Always represent PD	Incorporated into tumor burden
New, non-measurable lesions (i.e., < 5mm)	Always represent PD	Does not define progression (but precludes irCR)
Non-index lesions	Changes contribute to defining best overall response (BOR) of CR, PR, SD, and PD	Contribute to defining irCR (complete disappearance required)
CR	Disappearance of all lesions in two consecutive observations not less than 4 week apart	Disappearance of all lesions in two consecutive observations not less than 4 week apart if single arm trial and primary endpoint only
PR	> or = 30% decrease in the sum of the diameters of all index lesions compared with baseline in two observations at least 4 week apart, in absence of new lesions or unequivocal progression of non-index lesions	≥ 30% decrease in tumor burden compared with baseline in two observations at least 4 week apart if single arm trial and primary endpoint only
SD	< 30% decrease in sum of longest diameters of all index lesions compared with baseline cannot be established nor < 20% increase compared with nadir, in the absence of new lesions or unequivocal progression of non-index lesions	< 30% decrease in tumor burden compared with baseline cannot be established nor < 20% increase compared with nadir
PD	At least 20% increase in the sum of the longest diameters of index lesions and/or unequivocal progression of non-index lesions	At least 20% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 week apart

	RECIST 1.1	irRC RECIST 1.1
Handling of lymph nodes	Lymph nodes are considered pathologically enlarged if > 10 mm in SAD. To be measurable, nodal lesions must be ≥ 15 mm in SAD. Nodal lesions with SAD > 10 mm and < 15 mm are non- measurable. The sum of the diameters (LD for extranodal target lesions, SAD for nodal lesions) is followed through the course of therapy	Not differentiated from other tumor measurements

Derivation of irRC Overall Responses
(Modified for RECIST 1.1. Criteria)

Measurable response	**Non-measureable response**		**Overall response**
Index and new, measurable lesions (tumor burden)* %	Non-index lesions	New, non-measurable lesions	Using irRC
↓ 100	Absent	Absent	irCR/\
↓ 100	Stable	Any	irPR/\
↓ 100	Unequivocal progression	Any	irPR/\
↓ ≥ 30	Absent/ Stable	Any	irPR/\
↓ ≥ 30	Unequivocal progression	Any	irPR/\
↓ <30 to <20↑	Absent/ Stable	Any	irSD
↓ <30 to <20↑	Unequivocal progression	Any	irSD
≥ 20↑	Any	Any	irPD/\

*Decreases assessed relative to baseline, including measurable lesions only (>5 x 5 mm).

/\Assuming response (irCR or irPR) and progression (irPD) are confirmed by a second consecutive assessment at least 4 weeks apart.

Defining immune-related Response Criteria by RECIST 1.1 criteria at 20 weeks (irDCR at 20 weeks):

1. Any patient with stable disease or progressive disease at any time in the trial with "rapid clinical deterioration" felt to be related to disease progression is irPD

2. Any patient who meets the criteria for RECIST 1.1 CR at 20 weeks is irCR

3. Any patient who meets the criteria for RECIST 1.1 PR at 20 weeks is irPR

4. Any patient who meets the criteria for RECIST 1.1 SD at 20 weeks is irSD

5. A patient with RECIST 1.1 PD but no rapid clinical deterioration may stay on study if his/her next tumor measurement evaluation is stable disease or better.

6. If patient has first time PD by RECIST 1.1 criteria, call it unconfirmed PD for irRC RECIST 1.1.

7. A patient with unconfirmed irPD at 20 weeks whose next tumor measurement is SD or better will be considered to be included in the irDCR at 6 months.

8. A patient with unconfirmed irPD at 20 weeks who fails to qualify for RECIST 1.1 SD or unconfirmed CR or PR by next tumor measurement will be considered to have RECIST 1.1 PD and irPD at 20 weeks.