Cover Page for Protocol – J1790

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Official title of study	A Randomized Phase 2 Study of the Safety, Efficacy, and Immune Response of CRS-207, Nivolumab, and Ipilimumab with or without GVAX Pancreas Vaccine (with Cyclophosphamide) in Patients with Previously Treated Metastatic Pancreatic Adenocarcinoma
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Johns Hopkins Protocol #: J1790, IRB00137389

BMS Protocol #: CA209-9LM

Principal Investigator: Dr. Dung Le (Protocol Chair)

[redacted]

IND Sponsor: Dr. Elizabeth Jaffee

[redacted]

IND: BB IND 16147

Bristol-Myers Squibb Supplied Agent: Nivolumab (BMS-936558; anti-PD-1 mAb)
Ipilimumab (BMS-734016; anti-CTLA-4 mAb)

Johns Hopkins University Supplied Agent: GVAX pancreas vaccine
(Panc 10.05 pcDNA-1/GM-Neo, Panc 6.03 pcDNA-1/GM-Neo);
CRS-207 (*Lm* Δ*actA*/Δ*inlB*/hMesothelin)

Commercial Agent: Cyclophosphamide (CY, Cytoxan®)

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TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objective

To determine the objective response rate (ORR) using Response Evaluation Criteria for Solid Tumors (RECIST 1.1) in two cohorts of subjects with previously treated metastatic pancreatic cancer: Arm A treated with cyclophosphamide (CY)/ nivolumab/ipilimumab/GVAX pancreas vaccine followed by nivolumab/ipilimumab/ CRS-207 and Arm B treated with nivolumab/ipilimumab/CRS-207.

1.2 Secondary Objective

1.2.1 To assess safety and characterize toxicities of each vaccine treatment regimen when combined with anti-PD-1 and anti-CTLA-4 blockade in subjects with metastatic pancreatic adenocarcinoma.

1.3 Exploratory Objectives

1.3.1 To assess the overall survival (OS).

1.3.2 To assess progression free survival (PFS), duration of response (DOR), and time to progression (TTP) by RECIST 1.1.

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

1.3.4 To assess the ORR, PFS, and DOR by immune-related response criteria (irRC).

1.3.5 To collect peripheral blood mononuclear cells (PBMC), plasma, and serum to identify potential therapeutic targets, 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 cell phenotyping 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 anti-thyroglobulin and anti-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.

1.3.6 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.
- Next-generation sequencing of T cell receptor (TCR) genes may be used to compare the tumor infiltrating T cell repertoire in responders and 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.

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

- Microbial community analysis 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 nivolumab and ipilimumab in combination with either sequential administration of CY/GVAX pancreas vaccine followed by CRS-207 (Arm A) or with administration of CRS-207 alone (Arm B) in subjects with metastatic pancreatic adenocarcinoma who have progressed after at least 1 prior chemotherapy regimen. The primary endpoint of this study is objective response rate (ORR) using RECIST 1.1. Approximately 63 subjects will be enrolled and randomized 1:1 to the two treatment arms to achieve 60 treated subjects (i.e. allowing for 5% loss).

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

Table 1: Treatment Schedule

TREATMENT SCHEDULE					
Arm	**CY**	**Nivolumab**	**Ipilimumab**	**GVAX**	**CRS-207**
A	Day 1, Cycles 1, 2	Day 1, Cycles 1, 2, 3, 4, 5, 6	Day 1, Cycles 1, 3, 5	Day 2, Cycles 1, 2	Day 2, Cycles 3, 4, 5, 6
B	None	Day 1, Cycles 1, 2, 3, 4, 5, 6	Day 1, Cycles 1, 3, 5	None	Day 2, Cycles 1, 2, 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 18 weeks and courses can be repeated. The treatment schedule for Arms A and B can be found in **Table 1**. 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 60 subjects have received at least one dose of study treatment. It is estimated that 5% of the subjects will not receive treatment, so approximately 63 subjects will be randomized to achieve 30 treated subjects in Arm A and 30 treated subjects in Arm B. If the investigator assesses a drug-related toxicity (that requires discontinuation) to be related to an individual component of the treatment schedule, dosing for that study drug alone may be discontinued while dosing is delayed until the subject meets criteria to resume treatment of the other study drugs. The relationship to the discontinued study drug should be well documented in the source documents and permission from the Protocol Chair needs to be obtained prior to continuation with the other study drugs.

The proportion of treated subjects with unacceptable toxicity will be monitored using a Bayesian stopping guideline within each treatment arm separately. Once the first 12 participants have been randomized (6 in each group), accrual will be suspended until the toxicity levels have been determined to be acceptable in both arms (i.e. confirmation that less than 3 subjects experience unacceptable toxicities during the first 4 weeks of treatment). Then, the remaining participants will be enrolled and monitored routinely. Complete unacceptable toxicity criteria can be found in **Section 5.7**.

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 up to a maximum of 2 years, or until discontinuation due to unacceptable toxicity, lack of clinical benefit as determined by the investigator, subject withdrawal, or termination of the study by IND Sponsor. Subjects that begin a new course prior to the 2 year cut-off may complete that course prior to coming off study. 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 5.10**. Subjects will return to the study site 28 (±7) days 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 28 days 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 5.13**.

After completion of treatment and EOT assessments, all subjects, including those who did not receive treatment, will continue to be followed every three months (+/- 2 weeks) by telephone, e-mail, or optional clinic visit until death, withdrawal of consent, or closure of study. Subjects will also be contacted at 100 days (+14 day reporting window) from the last dose of nivolumab/ ipilimumab or 28 days (+7 day reporting window) from the last dose of cyclophosphamide, GVAX, or CRS-207 if the subject never received nivolumab/ipilimumab or is no longer receiving nivolumab/ipilimumab due to toxicity, whichever reporting period is longer. Information on survival and new cancer therapies will be collected. In addition, all subjects that received at least one dose of CRS-207 will be monitored for CRS-207 infection for one year per **Section 5.13**.

All subjects who discontinue study treatment should continue to be monitored for disease status by radiologic imaging every two months (+/- 2 weeks) until: 1) the start of a new antineoplastic therapy (information of the new cancer therapy will be collected), 2) disease progression, 3) death, 4) withdrawal of consent, or 5) the close of the study, whichever occurs first.

All subjects will be followed after their last dose of study drug for the development of adverse events (AEs) and serious adverse events (SAEs) as described in **Section 7.5.1**.

The primary analysis will be conducted when all treated subjects have documented response or progression by RECIST 1.1, or have discontinued the study. Information on survival may continue to be gathered for supplementary analyses after the completion of the primary analysis. 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.

2. BACKGROUND

2.1 Study Disease

Despite decades of basic and clinical research, effective therapy for the treatment of patients with pancreatic ductal adenocarcinoma (PAC) remains one of the greatest unmet clinical needs in oncology today. Currently, PAC accounts for approximately 7% of all cancer-related mortality and has the lowest 5-year survival rate among all cancer types in the United States. PAC is currently the 4th leading cause of death from cancer in the U.S. with estimates in 2016 for 53,070 people diagnosed and about 41,780 dying from the disease[1]. Worldwide it will claim more than 300,000 lives this year[2]. It is projected that by 2030, pancreatic cancer will become the second leading cause of cancer-related death in the US[3].

Most patients are initially diagnosed with advanced disease that is inoperable with median survival of less than 1 year. Patients with advanced disease are usually treated with chemotherapy, with the intent of prolonging survival and palliating symptoms (pain, weight loss and decrease in performance status). From 1997, gemcitabine was the standard chemotherapy for advanced pancreatic cancer after demonstrating a significant improvement in survival compared to 5-

fluorouracil (5-FU)[4]. Median survival was 5.65 months for gemcitabine-treated patients and 4.41 months for 5-FU treated patients, while overall tumor response rates were 5.4% and 0%, respectively.

Until recently, only erlotinib, an oral epidermal growth factor (EGF) inhibitor, was shown in a Phase 3 study to modestly improve median OS in combination with gemcitabine over gemcitabine alone (6.24 months for the doublet versus 5.91 months for gemcitabine alone) without a significant difference in ORR between the treatments[5]. In 2011, a Phase 2/3 trial conducted by a French consortium study group demonstrated FOLFIRINOX, a combined regimen of oxaliplatin, irinotecan, fluorouracil, and leucovorin significantly increased survival in patients with pancreatic cancer over gemcitabine alone. Median OS was 11.1 months versus 6.8 months for each treatment, respectively (hazard ratio [HR] for death, 0.57; 95% confidence interval [CI], 0.45 to 0.73; $p < 0.001$). The ORR was also increased to 31.6% from 9.4% ($p < 0.001$). Adverse events were increased in the FOLFIRINOX group and 5.4% of patients in this group experienced febrile neutropenia[6]. Although FOLFIRINOX represents an efficacious regimen in pancreatic cancer, there are still concerns about its potential toxicity and it is being reserved for the most fit patients.

In the MPACT (**M**etastatic **P**ancreatic **A**denocarcinoma **C**linical **T**rial) study, *nab*-paclitaxel combined with gemcitabine demonstrated a statistically significant and clinically meaningful median OS of 8.5 versus 6.7 months (HR 0.72, $p < 0.0001$ including a 59% increase in one-year survival (35% versus 22%, $p=0.0002$) and demonstrated double the rate of survival at two years (9% versus 4%, $p=0.02$) as compared to gemcitabine alone in previously untreated patients with metastatic pancreatic cancer. *nab*-/gemcitabine also demonstrated a statistically significant improvement in key secondary endpoints compared to gemcitabine alone, including a 31% reduction in the risk of progression or death with a median PFS of 5.5 versus 3.7 months (HR 0.69, $p < 0.0001$) and an ORR of 23% compared to 7% (response rate ratio of 3.19, $p < 0.0001$)[7]. The MPACT study and regimen formed the basis for full FDA approval in September 2013 for the first-line treatment of metastatic adenocarcinoma of the pancreas.

Nanoliposomal irinotecan in combination with 5-FU was recently approved for patients with previously treated pancreatic cancer. However, it is unknown if this combination is better than 5-FU and irinotecan (FOLFIRI) as 5-FU was the comparator and there was no benefit in patients who previously received irinotecan so the value of this drug is questionable in FOLFIRINOX treated patients[8]. Therapies for patients with metastatic pancreatic cancer are urgently needed.

Novel approaches, such as immunotherapy, hold promise in this very difficult cancer.

2.2 Rationale

Therapeutic benefit of immunotherapy in pancreatic cancer remains to be seen. Single agent therapy using vaccines to induce antigen-specific T cells or targeting immune checkpoints such as programmed death-1 (PD-1) or cytotoxic T-lymphocyte associated protein-4 (CTLA-4) does not address the complex immunosuppressive mechanisms at play both at the systemic level and in the tumor microenvironment. Effective immunotherapy in pancreatic cancer may require combinations of 2 or more agents to overcome this tolerance. Various combination strategies are being tested in less immunogenic tumors. CTLA-4 or PD-1 inhibition with pancreatic cancer vaccines is currently being studied with GVAX Pancreas (allogeneic pancreatic cancer cells modified to express GM-CSF) and CRS-207 (attenuated *Lm* expressing the tumor associated

antigen mesothelin). In each of these studies, there have been a handful of objective responses but in general pancreatic cancer has been refractory to immunotherapy and triplet approaches may be necessary. Numerous studies are targeting various immune checkpoints and stimulatory agonists but it could possibly be futile without a vaccine to induce infiltration of an inflammatory infiltrate including effector T cells into the tumor.

Immunotherapies in Pancreatic Cancer

Nivolumab

[redacted]

Nivolumab Dose Selection

[redacted]

Ipilimumab

[redacted]

[redacted]

Dual Blockade with Nivolumab and Ipilimumab

[redacted]

3. PATIENT SELECTION

3.1 Inclusion Criteria

3.1.1 Age ≥18 years.

3.1.2 Have histologically- or cytologically-proven ductal adenocarcinoma of the pancreas. Patients with mixed histology (>30% non-adenocarcinoma component) will be excluded.

3.1.3 Have metastatic disease.

3.1.4 Have documented radiographic disease progression at the time of study enrollment, after previous systemic chemotherapy given in a neoadjuvant, adjuvant, locally advanced or metastatic setting.

3.1.5 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 Patient's 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 Adequate organ and marrow function as defined below:

– Leukocytes	≥ 3,000/mcL
– Absolute neutrophil count	≥ 1,500/mcL
– Lymphocyte count	≥ 800/mcL
– Platelets	≥ 100×10^3/uL
– 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):

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

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

– 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.** Patients with a positive HCG due to tumor secretion may be permitted to enroll if lack of pregnancy can be documented (e.g. transvaginal ultrasound or serial HCG) and with approval by the Protocol chair.

- 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 5 months 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 7 months 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 prophylactic vaccine within 14 days of first dose of study drug (7 days for the COVID vaccine) or received a live vaccine within 30 days of planned start of study therapy.

3.2.7 Patients with a history of prior treatment with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA4 antibodies.

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

3.2.9 Use more than 2 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 has not and 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 Evidence of clinical ascites. Trace or small amounts of radiographic ascites may be approved by the Protocol Chair.

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 may be approved by the Protocol Chair).

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 Subjects with active, known or suspected autoimmune disease. Subjects with Graves or Hashimoto's disease, vitiligo, type I diabetes mellitus, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of

an external trigger are permitted to enroll.

3.2.22 Presence of any tissue or organ allograft, regardless of need for immunosuppression, including corneal allograft. Instances where loss of the graft is not a clinical concern (such as dental bone grafts or skin grafts placed only to promote skin growth) can be approved by the Protocol Chair. Patients with a history of allogeneic hematopoietic stem cell transplant will be excluded.

3.2.23 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.

3.2.24 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)

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

3.2.26 Patient is on supplemental home oxygen.

3.2.27 Patient has an unhealed surgical wound or ulcer, or a bone fracture considered non-healing.

3.2.28 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).

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

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

3.2.31 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.

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

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. REGISTRATION, RANDOMIZATION, AND BLINDING

4.1 General Guidelines

Eligible patients will be entered on study centrally at the Sidney Kimmel Comprehensive Cancer Center at the Johns Hopkins University by the Lead Study Coordinator. All sites should contact the Lead Study Coordinator to verify ongoing study enrollment. The Registration Form and Eligibility Checklist will be supplied to each participating site.

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

4.2 Registration Process

To register a patient, the following de-identified documents should be completed and sent to the Lead Study Coordinator at [redacted]

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

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

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

4.3 Randomization

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/ipilimumab/GVAX pancreas vaccine followed by nivolumab/ipilimumab/CRS-207) or Arm B (nivolumab/ipilimumab/CRS-207) in a 1:1 fashion using permuted blocks of varying sizes.

5. TREATMENT PLAN

5.1 Agent Administration

Treatment will be administered on an outpatient basis. Treatment schedule is described in **Section**

1.4. Dosing delays are described in **Section 6**. No investigational or commercial agents or therapies other than those described below in **Table 2** may be administered with the intent to treat the subject's malignancy.

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*	18 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; NS pre- and post-infusion to total 1500ml (suggested: 500ml pre and 1000ml post). Subjects may also be pre-medicated with anti-emetics (suggested: IV ondansetron and IV fosaprepitant).	1×10^9 CFU in 100ml NS	IV infusion over 1 hour**	
Nivolumab	No prophylactic pre-medication will be given unless indicated by previous experience in an individual subject per **Section 5.3.4**.	360 mg	IV infusion over 30 min*	
Ipilimumab	No prophylactic pre-medication will be given unless indicated by previous experience in an individual subject per **Section 5.3.4**.	1 mg/kg	IV over 30 minutes*	

*Infusion times are approximate (- 10/ + 15 min) and may need to be adjusted based on subject tolerability.
**Infusion times are approximate (± 15 min) and may need to be adjusted based on subject tolerability.

Please see **Section 6.2** for guidance regarding dosing delays. If the investigator assesses a drug-related toxicity (that requires discontinuation) to be related to an individual component of the treatment schedule, dosing for that study drug alone may be discontinued while dosing is delayed until the subject meets criteria to resume treatment of the other study drugs. The relationship to the discontinued study drug should be well documented in the source documents and permission from the Protocol Chair needs to be obtained prior to continuation with the other study drugs.

5.1.1 Cyclophosphamide (CY)

Subjects may be pre-medicated prior to administration with anti-emetics per institutional

guidelines. Subjects should be observed for a minimum of 30 minutes before administration of nivolumab. Acute reactions resulting in the delay of nivolumab or ipilimumab will be managed using standard therapy for acute drug reactions as per institutional standard of care and reported to the Protocol Chair 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

Use of Central Lines

[redacted]

[redacted]

5.1.4 Nivolumab

[redacted]

5.1.5 Ipilimumab

[redacted]

Antiemetic medications should not be routinely administered prior to dosing of drugs. See **Section 5.2.4** for subsequent premedication recommendations following an ipilimumab-related infusion reaction.

5.2 General Concomitant Medication and Supportive Care Guidelines

5.2.1 Cyclophosphamide (CY)

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

5.2.2 GVAX Pancreas Vaccine

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

5.2.3 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. Grade 3 or greater creatinine, AST, ALT, and bilirubin should be repeated within 24-72 hours as well.

5.2.4 Nivolumab and Ipilimumab

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

5.2.4.1 Infusion Reactions

Since nivolumab and ipilimumab contain 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 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 or ipilimumab 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 or ipilimumab 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 or ipilimumab 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 or ipilimumab 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 or ipilimumab. 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 and ipilimumab 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 ipilimumab, GVAX and CRS-207 treatment delays following a nivolumab or ipilimumab infusion-related reaction.

5.2.4.2 Nivolumab and Ipilimumab-Related Adverse Events

Blocking PD-1 or CTLA-4 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 and ipilimumab studies.

For the purposes of this study, a nivolumab or ipilimumab-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 or ipilimumab-related AEs must be documented on an AE or SAE CRF. Identification and treatment of nivolumab and ipilimumab-related AEs can be found in **Appendix B**. Additional guidance can be found in the nivolumab and ipilimumab Investigator's Brochures (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 or ipilimumab-related AE (**Section 5.5**).

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

5.3 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)
- Any major surgery or surgical procedure; if required must be discussed with the Protocol Chair to determine if it is appropriate for the subject to continue study treatment
- TNF pathway inhibitors or PI3 kinase inhibitors
- Another investigational agent
- Filgrastim (Neupogen® or G-CSF) or sargramostim (Leukine® or GM-CSF)
- Live vaccines (examples of live vaccines include, but are not limited to: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid [oral] vaccine). Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.
- The use of anticoagulants is known to increase the risk of gastrointestinal hemorrhage. Since gastrointestinal hemorrhage is an adverse reaction with nivolumab, subjects who require concomitant anticoagulant therapy should be monitored closely.
- 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.
- Palliative (limited-field) radiation therapy is permitted, but only for pain control and with approval by the Protocol Chair or IND Sponsor.
- Systemically active steroids can be used but should be reported to the Protocol Chair and/or IND Sponsor. Steroid treatment should be completed at least 14 days prior to resuming study-related treatments. Patients requiring adrenal replacement steroid doses ≤ 10 mg daily prednisone equivalent (in the absence of active autoimmune disease) may resume treatment if approved by the Protocol Chair or the IND Sponsor. Patients requiring replacement doses of steroids are required to discontinue treatment with CRS-207.
- If steroids or immunosuppressive agents are required during treatment, prophylactic antibiotics will be administered as outlined in **Section 5.5.**

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 for a subject to continue dosing if therapy is given concurrently with study participation:

- General anesthesia
- Aspirin >325 mg/day (chronic daily use of aspirin ≤325 mg/day and heparin flushes for central lines are allowed except during CRS-207 infusions through 4 days after each CRS-207 infusion.)
- More than 3 g/day of acetaminophen
- Systemic antibiotics

5.4 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 or IND Sponsor.

If subjects receive immunosuppressive medications on or after study, prophylactic antibiotics to prevent CRS-207 infection are strongly recommended for the duration of the treatment with the immunosuppressant [redacted]

5.5 Antibiotic Administration

[redacted]

[redacted]

Subjects with clinical or laboratory signs or symptoms of persistent 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 persistent 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.

5.6 Definition of an Overdose for this Protocol

Overdose of nivolumab or ipilimumab are 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, IND Sponsor (Dr. Elizabeth Jaffee), and Bristol-Myers Squibb (BMS). IND Sponsor, and BMS contact information can be found in **Section 7.5.1**.

5.7 Unacceptable Toxicity

Unacceptable toxicities are defined as:

1. Any treatment-related ≥ grade 3 AEs. Exceptions include:

    - Asymptomatic laboratory abnormalities
    - Grade 3 fatigue
    - Grade 3 dermatologic AEs that are considered mild in severity but only considered grade 3 because of >30% body surface involvement
    - Fever, chills, rigors, hypertension, hypotension, syncope, or hypoxia occurring within 12 hours of CRS-207 administration
    - Diarrhea, nausea, or vomiting that resolves to < grade 3 within 24 hours of intervention
    - Grade 3-4 hyperglycemia or grade 3 endocrinopathies where symptoms are controlled on hormone replacement therapy

2. Any of the following toxicities related to CRS-207:

    - A fever of >40°C that lasts for greater than 24 hours and does not respond to antipyretics.
    - Clinically significant hypotension unresponsive to IV fluids (e.g., systolic blood pressure [BP] <90 mm Hg or mean arterial pressure <55 mm Hg as measured on two separate occasions at least 10 minutes apart).
    - Initiation of antibiotic therapy, coincident with simultaneous isolation of CRS-207 from a normally sterile body site, other than blood (e.g., cerebrospinal fluid, joint fluid).

3. Treatment related blood bilirubin > 5 x ULN or concurrent blood bilirubin > 2 x ULN and AST or ALT > 3 x ULN

4. Treatment related eye pain ≥ grade 2 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.

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. Grade 3 or greater creatinine, AST, ALT, and bilirubin should be repeated within 24-72 hours as well.

The proportion of unacceptable toxicities will be monitored separately in each arm. If the toxicity levels in either treatment arm (A or B) are unacceptable, then enrollment will be suspended until

further review and consideration by the Protocol Chair, IND Sponsor, and the Medical Expert Committee (MEC). If treatment in one arm is permanently discontinued due to toxicity, the other arm may continue as long as the toxicity level remains acceptable. There will be no dose reductions for CY, nivolumab, ipilimumab, 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

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%	2.0%
15%	6.9%
20%	17.5%
25%	33.0%
30%	52.4%
35%	71.2%

5.8 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

5.8.1 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 5 months 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 7 months after the last dose of study drug.

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

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

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

5.8.2 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 5 months of completing treatment as well as any pregnancy in partners of male subjects throughout the study or within 7 months 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.

5.8.3 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.

5.8.4 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.

5.9 Duration of Therapy

Subjects on both arms will receive treatment every 3 weeks for 6 cycles of treatment within a course (18 weeks total). At the investigator's discretion, subjects who are clinically stable and meet dosing requirements (per **Section 6.2**) at the end of the first course may receive additional courses of their assigned treatment for up to a maximum of 2 years. Subjects that begin a new course prior to the 2 year cut-off may complete that course prior to coming off study. The additional course(s) may start as early as 3 weeks (+7 days) 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

5.10 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 5.7**). Exceptions for treatment discontinuation are listed in **Section 5.10.2**. If the study treatment has provided clinical benefit (as defined in **Section 5.10.1**), the IND sponsor may approve trial continuation for patients experiencing toxicities that are not life threatening or of major clinical concern (such as pruritis or transient hypotension).
- Disease progression as defined in **Section 5.10.1**
- Severe or life-threatening nivolumab or ipilimumab-related AE(s) (see **Section 5.10.2**)
- Need for >2 dose delays due to the same drug-related 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

5.10.1 Disease Progression

GVAX Pancreas vaccine, CRS-207, nivolumab, and ipilimumab 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[16].

Subjects will be permitted to continue with treatment beyond 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:

- 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 documented in the study records.

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

5.10.2 Nivolumab and Ipilimumab-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, and BMS must be notified in the event of these AEs):
    - Any grade 2 treatment-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks of starting therapy OR requires systemic treatment
    - Any grade 3 non-skin, drug-related AE lasting > 7 days, with the following exceptions:
        - Grade 3 treatment-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reaction, or infusion reaction (applies to nivolumab and ipilimumab only) of any duration requires discontinuation
        - Grade 3 treatment-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
        - Grade 3 treatment-related laboratory abnormalities do not require treatment discontinuation except:
            - Grade 3 treatment-related thrombocytopenia > 7 days OR that is associated with bleeding requires discontinuation
            - Any treatment-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
                - Total bilirubin > 3 × 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 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 within 72 hours of their onset.

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

- Grade 4 lymphopenia and leukopenia.

- Grade 4 treatment-related endocrinopathy adverse events, such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Protocol Chair.

- 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 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. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Protocol Chair 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 or nivolumab/ipilimumab 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 and ipilimumab IB might be considered for individual cases.

Subjects that are required to stop treatment with nivolumab/ipilimumab 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/ipilimumab-related toxicity(s) has resolved to a grade 1.

5.11 End of Treatment (EOT) Visit

All subjects will return to the study site 28 days (± 7 days) after the final study treatment (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 5.12 and 10.0** as appropriate.

If the EOT visit occurs early (e.g., 1 week prior to the expected visit as protocol allows) or if the patient cannot return due to disease progression, 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]

5.12 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 EOT visit. Subjects will be contacted every three months (+/- 2 weeks) 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. Subjects will also be contacted at 100 days (+14 day reporting window) from the last dose of nivolumab/ipilimumab if the subject was still receiving nivolumab/ipilimumab at the time of treatment discontinuation to monitor drug toxicity. In addition, all subjects that received at least one dose of CRS-207 will be monitored for CRS-207 infection for one year per **Section 5.13**.

Subjects who discontinued study treatment without documented disease progression should continue to be monitored for disease status by radiologic imaging. Disease monitoring should continue to be assessed every two months (+/- 2 weeks) until: 1) start of a new antineoplastic therapy (information of the new cancer therapy will be collected), 2) disease progression, 3) death, 4) withdrawal of consent, or 5) study closure, whichever occurs first.

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 after their last dose of study drug for the development of AEs and SAEs as described in **Section 7.5.1**

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 visit prior to transitioning to participation in the separate long-term follow-up study.

5.13 Blood Cultures for CRS-207 Surveillance

[redacted]

5.13.1 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 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 the IND Sponsor or designee 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.

5.13.2 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 (peripheral and port for those with indwelling ports), 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 must be notified immediately, and the duplicate samples and Listeria isolate must be sent to the IND Sponsor 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, nivolumab, and ipilimumab will not be permitted.

6.2 Dosing Delays

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 < 7.5 g/dL
- ANC < 1000/uL
- Platelets < 80 × 10^3/uL

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 must be contacted for further instructions on continued treatment. Additional delays or modifications to the treatment schedule must be approved by the Protocol Chair or IND Sponsor.

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

- Nivolumab and ipilimumab-related infusion reactions must resolve to baseline prior to administration of ipilimumab, GVAX, or CRS-207.
- If a nivolumab-related infusion reaction prevents subsequent infusion of ipilimumab on the same day, the dose of ipilimumab should be replaced within 72 hours. In such instances, at least 18 days must elapse between the replacement dose of ipilimumab and the administration of the next dose of nivolumab combined with ipilimumab. If the dose of ipilimumab cannot be replaced within 72 hours, resume ipilimumab at the next scheduled dose per **Section 10**.
- Resume Day 2 treatment schedule (GVAX or CRS-207) and assessments without repeating Day 1 study treatments (CY and/or nivolumab/ipilimumab) 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 2 weeks from the previous Day 1 treatment. This includes steroid treatment requiring at least a 14 day washout prior to resuming study-related treatments.

Administration of study drug should be delayed for the following:

- Dosing criteria are not met
- Any grade ≥ 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 ≥3 skin treatment-related AE
- Any ≥ 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 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 and ipilimumab IB might be considered for individual cases.

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

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

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.

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. Additionally, expected progression of the disease being studied will not be recorded as an adverse event.

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 (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 (AESI)

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, the event should be reported to the IND 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, package insert, safety reports or informed consent is considered "unexpected".

Expected (known) AE: An AE, which has been reported in the IB, package insert or safety reports. 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, nivolumab, or ipilimumab. 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 related and unrelated) will be captured on the appropriate study-specific CRFs. All AEs experienced by subjects will be collected and reported from the first dose of the investigational agent, throughout the study, and will be followed for 28 days after last dose of study drug unless related to the investigational agent.

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

Report AEs to the Protocol Chair and IND Sponsor within 24 hours once identified as an unacceptable toxicity (defined in Section 5.7).

Elizabeth Jaffee: [redacted]
Dung Le:

Report all AESI to the Protocol Chair and IND Sponsor within 24 hours once identified (defined in Section 7.1.3):

Elizabeth Jaffee: [redacted]
Dung Le:

All SAEs (including deaths) occurring from the first dose of the study drug through 100 days (+ 14 day reporting window) after the last dose of nivolumab or ipilimumab or within 7 days prior to initiation of a new antineoplastic treatment (whichever comes first) will be collected and reported. If the subject never received or is no longer receiving nivolumab or ipilimumab due to toxicity, all SAEs (including deaths) occurring from the first dose of the study drug through 28 days from the last dose of cyclophosphamide, GVAX, or CRS-207 (whichever reporting period is longer). All SAEs (including deaths) that the investigator considers related to study drug occurring after the follow-up periods must be reported.

Subjects who have an ongoing AE/SAE 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.

SAEs will be reported promptly to the IND Sponsor, and BMS within 24 hours of initial notification of the SAE. If this falls on a weekend or holiday, an email notification is acceptable but must be followed by an SAE reporting form on the next business day.

SAE reports and any other relevant safety information are to be sent to:

Elizabeth Jaffee: [redacted]
Dung Le:
BMS:

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
- Death

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

7.5.3 Reconciliation of SAEs

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

7.5.4 Overdose

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

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 5 months 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 7 months 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 SAE form with the seriousness category checked as 'other important medical event'. When the form is completed, the IND Sponsor and BMS will be notified of the event.

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 the IND Sponsor and BMS. 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 the IND Sponsor and BMS.

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

Participating sites will be responsible for reporting to their IRB and IBC. Serious adverse events will be reported to the IRB and IBC per institutional standards. Upon receipt, follow-up information will be given to the IRB and IBC (as soon as relevant information is available) per institutional standards.

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

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

8.2.1 Agent Accountability

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

8.2.2 Mode of Action

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

8.2.3 Description

[redacted]

8.2.4 Packaging and Labeling Information

[redacted]

8.2.5 Preparation

[redacted]

8.2.6 Storage

[redacted]

8.2.7 Stability

[redacted]

8.2.8 Route of Administration

[redacted]

8.2.9 Subject Care Implications

[redacted]

8.2.10 Returns and Reconciliation

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

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

8.3 CRS-207

8.3.1 Agent Accountability

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

8.3.2 Mode of Action

[redacted]

8.3.3 Description

[redacted]

8.3.4 Packaging and Labeling Information

[redacted]

8.3.5 Preparation

[redacted]

8.3.6 Storage

[redacted]

8.3.7 Stability

[redacted]

8.3.8 Route of Administration

[redacted]

8.3.9 Subject Care Implications

[redacted]

8.3.10 Returns and Reconciliation

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

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

8.4 Nivolumab

8.4.1 Agent Accountability

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

At the end of the study period, Bristol-Myers Squibb Company will not continue to supply study drug to subjects/investigators unless the Sponsor-Investigator chooses to extend their study. The investigator is responsible to ensure that the subject receives appropriate standard of care or other appropriate treatment in the independent medical judgement of the Investigator to treat the condition under study.

8.4.2 Mode of Action

Nivolumab is a fully human monoclonal immunoglobulin (Ig) G4 antibody that binds to the PD-1 cell surface membrane receptor, a negative regulatory molecule expressed by activated T and B lymphocytes. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T cell responses to both foreign antigens as well as self-antigens.

8.4.3 Description

8.4.4 Packaging and Labeling Information

8.4.5 Preparation

8.4.6 Storage

8.4.7 Stability

8.4.8 Route of Administration

[redacted]

8.4.9 Subject Care Implications

[redacted]

8.4.10 Returns and Reconciliation

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

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

8.5 Ipilimumab

8.5.1 Agent Accountability

The IND Sponsor or the IND Sponsor's representative shall take responsibility for and

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

At the end of the study period, Bristol-Myers Squibb Company will not continue to supply study drug to subjects/investigators unless the Sponsor-Investigator chooses to extend their study. The investigator is responsible to ensure that the subject receives appropriate standard of care or other appropriate treatment in the independent medical judgement of the Investigator to treat the condition under study.

8.5.2 Mode of Action

Ipilimumab is a fully human immunoglobulin ($IgG_1\kappa$) that is specific for the CTLA-4 antigen expressed on a subset of activated T-cells. CTLA-4 interaction with the B7 molecule, one of its ligands expressed on professional antigen presenting cells, can down-regulate T-cell response. Ipilimumab is, thought to act by blocking the interaction of CTLA-4 with the B7 ligand, resulting in a blockade of the inhibitory effect of T-cell activation. The CTLA-4/B7 creates the interaction.

8.5.3 Description

[redacted]

[redacted]

8.5.4 Packaging and Labeling Information

[redacted]

8.5.5 Preparation

[redacted]

8.5.6 Storage

[redacted]

8.5.7 Stability

[redacted]

8.5.8 Route of Administration

[redacted]

8.5.9 Subject Care Implications

[redacted]

8.5.10 Returns and Reconciliation

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

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

9. CORRELATIVE/SPECIAL STUDIES

Research samples will be collected at the discretion of the PI based on availability of supplies and safety of patient and staff. 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 3 (4-6 cores per time point). If a biopsy was done within 21 days before first dose, archived tissue from this biopsy may be used as baseline sample. Fine needle aspiration will not be acceptable. Additional optional biopsies may be obtained later in the course of study treatment.

Attempts will be made to obtain archived tissue samples from all subjects. Archived FNA biopsy samples do not contain sufficient tissue and will not be collected.

Detailed instructions for tissue collection, processing, storage, 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 3) will be compared. PD-L1 expression may predict response to anti-PD-1[18,19]. 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. Dependent on availability of paired tissue samples, additional analysis including determination of gene signatures of tumor and immune cells will be performed to look for patterns of response associated with immune activation and changes in the tumor.

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 Cycles 1, 2, 4, and 6 only during Course 1. Pre- and post-treatment changes in PBMCs including effector, helper, and regulatory T cells, NK cells, and macrophages through cell phenotyping analysis and gene expression profiling will be measured. In addition, induction of Listeria and mesothelin antigen-specific T cell responses and changes to the T cell epitope repertoire will also be evaluated.

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 collection, processing, storage, and shipment 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 only during Course 1. Additionally, subjects will have whole blood for serum drawn 20-26 hours post-CRS-207 infusion during Cycles 3-6 for patients in Arm A and during Cycles 1-6 for patients in Arm B only during Course 1. Plasma will be collected prior to dosing on Day 1 of Cycles 1, 2, 4, 6, and the EOT evaluation only during Course 1. Humoral immune responses, including anti-Lm, anti-mesothelin, anti-thyroglobulin and anti-galectin 3 antibodies will be evaluated by using enzyme-linked immunosorbent assay (ELISA). 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 collection, processing, storage, and shipping are provided in the Laboratory Manual.

9.4 Stool and Oral Wash Samples Studies

Stool and oral wash specimens (and questionnaire) will be obtained when available. All stool specimens should be collected within 72 hours (and ideally within 24 hours) of the patient's appointment. Baseline specimens may be obtained at Cycle 1 Day 1 ± 30 days of Course 1. Additional samples will be collected at Course 1 Cycle 4 Day 1 (± 30 days), Course 1 Cycle 6 Day 1 (± 30 days) and EOT (± 30 days). Additional samples may be obtained if the patient has any drug-related toxicity or at other timepoints of interest at the discretion of the PI at any point during the trial.

Microbial DNA will be isolated from stool and oral wash 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 and oral wash collection, storage, and shipment 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.

9.6 Genomic Analysis

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

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

Clinical analysis. Several CLIA-certified laboratories now offer molecular profiling of cancer specimens in commercial and noncommercial settings and provide these results to patients and their physicians (e.g. Foundation Medicine, PGDx, Michigan Center for Translational Pathology, or JHU CLIA Laboratories). It is possible, therefore, that some of our research analyses will be conducted in these CLIA-certified environments. If tissue or cells are evaluated with next generation sequencing strategies to provide a molecular profile of individual cancer specimens in a CLIA-certified facility, these results will be made available to the patient and their physician. Patient confidentiality will be maintained, and the patient's identity will not be publicly linked to any study results. Researchers may use the data set generated in the CLIA assay setting to study genetic alterations across a large number of genes important in cancer. Germline mutations are only identified in punitive cancer genes. Researchers will use the data set for exploratory research to study cancer cell heterogeneity. Some of the sequencing data obtained from the NGS strategies will be uploaded to government sponsored databases, such as GEO and dbGAP. The results of the research studies may be published but subjects will not be identified in any publication.

If a germline alteration of clinical importance (as judged by the Investigator) to the subject and his or her family members is identified by a CLIA-certified test in the course of this analysis, attempts will be made in writing to contact the subject and/or family members for genetic counseling referral.

10. STUDY CALENDAR

10.1 Treatment Arm A

Study Procedures	Pre-Study	Cycle 1[24]			Cycle 2				Cycle 3				Cycle 4				Cycle 5				Cycle 6				EOT[26]
		D1	D2	D4[25]	D1	D2	D4[25]	D9[27]	D1	D2	D3	D9	D1	D2	D3	D9	D1	D2	D3	D9	D1	D2	D3	D9	
Visit Windows (days)[1]	-21 to D1	-	-	±1	- 2	-	±1	±1	- 2	-	-	±1	- 2	-	-	±1	- 2	-	-	±1	- 2	-	-	±1	+/- 7
CY[2]		X			X																				
Nivolumab[2]		X			X				X				X				X				X				
Ipilimumab[2]		X							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[3]	X																								
Con Meds, Adverse Events		X	X	X	X	X	X	X[27]	X	X	X	X[25]	X	X	X	X[25]	X	X	X	X[25]	X	X	X	X[25]	X
Physical Exam, ECOG PS[4]	X	X			X			X[27]	X				X				X				X				X
Vitals, Weight, & Height[5]	X	X	X		X	X		X[27]	X	X			X	X			X	X			X	X			X
Hematology, Chemistry[6, 12]	X	X			X			X[27]	X		X	X	X		X	X	X		X	X	X		X	X	X
Endocrine[7, 12]		X			X				X				X				X				X				X
Urinalysis[8, 12]	X																								
CD4, 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				

Study Procedures	Pre-Study	Cycle 1[24]			Cycle 2				Cycle 3				Cycle 4				Cycle 5				Cycle 6				EOT[26]
		D1	D2	D4[25]	D1	D2	D4[25]	D9[27]	D1	D2	D3	D9	D1	D2	D3	D9	D1	D2	D3	D9	D1	D2	D3	D9	
ECG[13]	X																								
CT/MRI, RECIST/irRC[14]	X												X												X
Vaccine Site Reactions[15]				X			X																		
Whole blood for PBMC[16, 29]		X			X								X								X				
Whole blood for plasma[16, 29]		X			X								X								X				
Serum[16, 29]		X			X				X		X		X		X		X		X		X		X		
Stool, Oral Wash Samples[17, 29]	X												X								X				X
Microbiome Questionnaire[17]	X												X								X				X
HLA[18]		X																							
Archival Tissue[19, 29]	X																								
Tumor Biopsies[20, 29]	X								X																
Antibiotics[21,22]																								X[28]	X[28]
Blood sample for CRS-207 testing[23]																									X

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

1: If necessary, a scheduled cycle may be delayed for up to 1 week. Longer delays to be approved by the IND Sponsor or Protocol Chair.
2: Order of administration is CY, Nivolumab, and then Ipilimumab. Subjects should be observed for a minimum of 30 minutes between each infusion.
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, 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 and at the end of the infusion (-5/+ 15 minutes). Ipilimumab: vitals will be collected prior to and at the end of the infusion (-5/+ 15 minutes). CRS-207: vital signs will be obtained prior to and then every 30 minutes (± 15 minutes) during infusion and every hour (-5/+ 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, ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin, amylase, total protein, albumin, calcium, magnesium, and phosphate. LDH at baseline only. 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. Grade 3 or greater creatinine, AST, ALT, and bilirubin should be repeated within 24-72 hours as well.

7: TSH (Total T3 and free T4 if TSH abnormal and clinically indicated).

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.

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. 3-D CT scans and RECIST reads will not be used to determine eligibility at baseline. 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 by phone or email.

16: Up to 120 mL of whole blood for PBMC isolation 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. Approximately 20 mL of whole blood for plasma collection will be drawn as indicated. Approximately 5.0 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. Collection of whole blood for isolation of PBMCs, plasma, and serum will only be drawn during Course 1.

17: Stool and oral wash specimens (and questionnaire) will be obtained when available. All stool specimens should be collected within 72 hours (and ideally within 24 hours) of the patient's appointment. Baseline specimens may be obtained at Cycle 1 Day 1 ± 30 days of Course 1. Additional samples will be collected at Course 1 Cycle 4 Day 1 (± 30 days), Course 1 Cycle 6 Day 1 (± 30 days), and EOT (± 30 days). Additional samples may be obtained

if the patient has any drug-related toxicity or at other timepoints of interest at the discretion of the PI at any point during the trial. Detailed instructions for stool and oral wash 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: 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. Detailed instructions for tissue collection, processing and shipment are provided in the Laboratory Manual.

20: 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 3 (4-6 cores per timepoint). If a biopsy was done within 21 days before first dose, archived tissue from this biopsy may be used as baseline sample. The Cycle 3 biopsy has a ± 1 week window. Additional optional biopsies may be obtained later in the course of study treatment. Fine needle aspiration will not be acceptable. Biopsies will only be collected during the first course of study treatment. Detailed instructions for tissue collection, processing and shipment are provided in the Laboratory Manual.

21 [redacted]

22

23: Blood for CRS-207 culture will be collected at EOT (or within 4 weeks of the last dose of antibiotics if patients do not complete 6 cycles of treatment) to assess clearance of CRS-207. After last dose of CRS-207, blood will continue to be collected for CRS-207 culture at 3, 6, 9, and 12 months from last dose of CRS-207 (+/- 1 week window for each collection).

24: Cycle 1 Day 1 evaluations do not need to be repeated if they were conducted within 3 days of the pre-study evaluations. The additional course(s) may start as early as 3 weeks (+7 days) from last dose of previous course.

25: Day 4 and 9 (± 1 day) adverse event assessments may be conducted by telephone or email.

26: Subjects will return to the study site for 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 (or if the patient cannot return due to disease progression), 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 should be contacted by telephone or email at 100 days (+ 14 day reporting window) to assess for treatment related toxicities that occur in the follow-up period.

27: The first 6 subjects randomized to Arm A will return to the study site at Cycle 2, Day 9 for a focused physical examination, assessment of ECOG status, vitals, labs, concomitant medications and adverse events during Course 1 only.

28: Site personnel will contact the subject by telephone (prior to and within 3 days after completion) to facilitate compliance with antibiotic treatment and document in source.

29: Research samples will be collected at the discretion of the PI based on availability of supplies and safety of patient and staff.

10.2 Treatment Arm B

Study Procedures	Pre-Study	Cycle 1[23]				Cycle 2				Cycle 3				Cycle 4				Cycle 5				Cycle 6				EOT[25]
		D1	D2	D3	D9	D1	D2	D3	D9[24]	D1	D2	D3	D9	D1	D2	D3	D9	D1	D2	D3	D9	D1	D2	D3	D9	
Visit Windows (days)[1]	-21 to D1	-	-	-	+1	- 2	-	-	±1	- 2	-	-	±1	- 2	-	-	±1	- 2	-	-	±1	- 2	-	-	±1	+/- 7
Nivolumab[2]		X				X				X				X				X				X				
Ipilimumab[2]		X								X								X							
CRS-207			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[24]	X	X	X	X[24,26]	X	X	X	X[24]	X	X	X	X[24]	X	X	X	X[24]	X	X	X	X[24]	X
Physical Exam, ECOG PS[4]	X	X				X			X[26]	X				X				X				X				X
Vitals, Weight, & Height[5]	X	X	X			X	X		X[26]	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	X	X		X	X	X
Endocrine[7, 12]		X				X				X				X				X				X				X
Urinalysis[8, 12]	X																									
CD4, 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				
ECG[13]	X																									
CT/MRI, RECIST/irRC[14]	X													X												X
Whole blood for PBMC[15, 28]		X				X								X								X				
Whole blood for plasma[15, 28]		X				X								X								X				

Study Procedures	Pre-Study	Cycle 1[23]				Cycle 2				Cycle 3				Cycle 4				Cycle 5				Cycle 6				EOT[25]
		D1	D2	D3	D9	D1	D2	D3	D9[24]	D1	D2	D3	D9	D1	D2	D3	D9	D1	D2	D3	D9	D1	D2	D3	D9	
Serum[15, 28]		X		X		X		X		X		X		X		X		X		X		X		X		
Stool, Oral Wash Samples[16, 28]	X													X								X				X
Microbiome Questionnaire[16]	X													X								X				X
HLA[17]		X																								
Archival Tissue[18, 28]	X																									
Tumor Biopsies[19, 28]	X									X																
Antibiotics[20,21]																									X[27]	X[27]
Blood sample for CRS-207 testing[22]																										X

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

1: If necessary, a scheduled cycle may be delayed for up to 1 week. Longer delays to be approved by the IND Sponsor and/or Protocol Chair.
2: Order of administration is Nivolumab followed by Ipilimumab. Subjects should be observed for a minimum of 30 minutes between each infusion.
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, 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. Nivolumab: vitals will be collected prior to and at the end of the infusion (-5/+ 15 minutes). Ipilimumab: vitals will be collected prior to and at the end of the infusion (-5/+ 15 minutes). CRS-207: vital signs will be obtained prior to and then every 30 minutes (± 15 minutes) during infusion and every hour (-5/+ 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, ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin, amylase, total protein, albumin, calcium, magnesium, and phosphate. LDH at baseline only. 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. Grade 3 or greater creatinine, AST, ALT, and bilirubin should be repeated within 24-72 hours as well.

7: TSH (Total T3 and free T4 if TSH abnormal and clinically indicated).

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.

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. 3-D CT scans and RECIST reads will not be used to determine eligibility at baseline. 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: Up to 120 mL of whole blood for PBMC isolation 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. Approximately 20 mL of whole blood for plasma collection will be drawn as indicated. Approximately 5.0 mL of blood for serum for immune monitoring will be drawn as indicated. Day 3 blood draws should be taken between 20 and 26 hours after start of dosing. Collection of whole blood for isolation of PBMCs, plasma, and serum will only be drawn during Course 1.

16: Stool and oral wash specimens (and questionnaire) will be obtained when available. All stool specimens should be collected within 72 hours (and ideally within 24 hours) of the patient's appointment. Baseline specimens may be obtained at Cycle 1 Day 1 ± 30 days of Course 1. Additional samples will be collected at Course 1 Cycle 4 Day 1 (± 30 days), Course 1 Cycle 6 Day 1 (± 30 days), and EOT (± 30 days). Additional samples may be obtained if the patient has any drug-related toxicity or at other timepoints of interest at the discretion of the PI at any point during the trial. Detailed instructions for stool and oral wash collection and shipment are provided in the Laboratory Manual.

17: 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.

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. 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 3 (4-6 cores per timepoint). If a biopsy was done within 21 days before first dose, archived tissue from this biopsy may be used as baseline sample. The Cycle 3 biopsy has a ± 1 week window. Additional optional biopsies may be obtained later in the course of study treatment. Fine needle aspiration will not be acceptable.

Biopsies will only be collected during the first course of study treatment. Detailed instructions for tissue collection, processing and shipment are provided in the Laboratory Manual.

20 [redacted]

21

22: Blood for CRS-207 culture will be collected at EOT (or within 4 weeks of the last dose of antibiotics if patients do not complete 6 cycles of treatment) to assess clearance of CRS-207. After last dose of CRS-207, blood will continue to be collected for CRS-207 culture at 3, 6, 9, and 12 months from last dose of CRS-207 (+/- 1 week window for each collection).

23: Cycle 1 Day 1 evaluations do not need to be repeated if they were conducted within 3 days of the pre-study evaluations. The additional course(s) may start as early as 3 weeks (+7 days) from last dose of previous course.

24: Day 9 (± 1 day) adverse event assessments may be conducted by telephone or email.

25: Subjects will return to the study site for 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 (or if the patient cannot return due to disease progression), 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 should be contacted by telephone or email at 100 days (+ 14 day reporting window) to assess for treatment related toxicities that occur in the follow-up period.

26: The first 6 subjects randomized to Arm B will return to the study site Cycle 2, Day 9 for a focused physical examination, assessment of ECOG status, vitals, labs, concomitant medications and adverse events during Course 1 only.

27: Site personnel will contact the subject by telephone (prior to and within 3 days after completion) to facilitate compliance with antibiotic treatment and document in source.

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

11. STUDY ENDPOINTS

11.1 Primary Endpoint

The primary endpoint is ORR, which is defined as the proportion of subjects with PR or CR according to RECIST 1.1. Subjects who discontinue due to toxicity or clinical progression prior to post-baseline tumor assessments will be considered as non-responders. Subjects who discontinue for other reasons prior to their first dose of study drug will be replaced and not included in the primary efficacy analysis.

11.2 Secondary Endpoint

The secondary endpoint is as follows:

- Safety assessed by the following measures:
  - Number of patients who have grade 3 or higher drug-related toxicities
  - Frequency of drug-related toxicity by grade
  - Injection-site reactions (after GVAX pancreas vaccine injections only)
  - Nivolumab-related infusion reactions
  - Ipilimumab-related infusion reactions
  - CRS-207-related infusion reactions
  - Immune-related AEs
  - Unacceptable toxicities
  - Vital signs: BP, pulse, 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:

- Overall survival (OS), duration of response, PFS measured by RECIST, immune-related progression-free survival (irPFS), and time to progression (TTP).
  - Overall survival (OS) is defined as the number of months from the 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).
  - 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. PFS will be censored at the date of the last scan for subjects without documentation of disease progression at the time of analysis.
  - Duration of Response (DOR) is defined as the number of months from the first documentation of a response to date of disease progression.

  - 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). It differs from PFS in that it does not include death in the definition of an event. TTP will be censored at the date of the last scan for subjects without documentation of disease progression at the time of analysis.
- Tumor marker kinetics measured by change in serum CA19-9 concentrations from baseline
- Objective disease responses, progression-free survival, 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
- Peripheral blood specimens, intratumoral core biopsy specimens, and resection specimens will be studied using a variety of laboratory techniques including but not limited to: immunohistochemistry (IHC), flow cytometry, CITE-Seq, RNA-Seq, whole exome sequencing, whole genome sequencing, T cell receptor and B cell receptor sequencing, ChIP-seq, ATAC-seq, and MBD-seq.

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)**.

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

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.

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 (Johns Hopkins University)

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 Safety Meetings

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

Monthly teleconferences will be scheduled to include the Coordinating Center and the clinical trial sites. During these meetings, the Coordinating Center and clinical trial sites shall discuss the following: study protocol updates, safety data, enrollment status, and progress of data for objectives.

12.3 Monitoring

The SKCCC Compliance Monitoring Program will provide external monitoring for JHU-affiliated sites in accordance with SKCCC DSMP (Version 6.0, 02/21/2019). The SMC Subcommittee will determine the level of patient safety risk and level/frequency of monitoring. Eligibility for all sites will be monitored by the Protocol Chair. Data monitoring of this protocol will occur on a regular basis with the frequency dependent on the rate of subject accrual and the progress of the study. Additional data and safety monitoring oversight will also be performed by the SKCCC Safety Monitoring Committee (SMC - as defined in the DSMP) and a Medical Expert Committee (MEC) as detailed below. The protocol will be monitored internally by the IND Sponsor and the Principal Investigator at each site. External monitoring will occur according to the following guidelines:

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

Participating site(s): The protocol will be monitored by the internal CRO at each site. A report of the reviews will be submitted to the Protocol Chair, IND Sponsor, and the SKCCC CRO.

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

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

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

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

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. 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.

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, 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.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

Sample size.

The primary endpoint is ORR, defined as the proportion of subjects with PR or CR according to RECIST 1.1. Subjects who discontinue due to toxicity or clinical progression prior to post-baseline tumor assessments will be considered as non-responders. Subjects who discontinue for other reasons prior to their first dose of study drug will be replaced and not included in the primary

analysis.

With a total of 30 evaluable subjects in each arm, the treatment will be considered successful if 5 or more subjects respond in a single arm. If the number of responses is 4 or less, the preliminary anti-tumor activity of the treatment will be rejected.

The study is powered to assess each arm separately. The sample size is based on an A'Hern single-stage phase 2 design[20]. A sample size of 30 evaluable subjects per arm are required to decide whether the proportion responding is less than or equal to 0.06 or greater than or equal to 0.22[21]. If the number of responses is 5 or more, the hypothesis that P <= 0.06 is rejected with a target error rate of 0.05 (alpha). If the number of responses is 4 or less, the hypothesis that P >= 0.22 is rejected with a target error rate of 0.20 (power = 0.80). Each arm will be evaluated independently.

The benchmark for the estimate of ORR is based on a recent study of metastatic pancreatic cancer patients who had failed one prior gemcitabine-based regimen where patients who received nanoliposomal irinotecan plus fluorouracil and folinic acid had a response rate of 16% (19/177). Response rates for patients receiving either nanoliposomal irinotecan monotherapy or fluorouracil and folinic acid were between 1-6%.

Statistical Analyses

Data will be summarized descriptively by treatment arm and overall. The descriptive summary including demographics and baseline variables will include counts and percentages for categorical variables and means, medians, standard deviations and minimum and maximum values for continuous variables.

Time-to-event outcomes such as OS will be analyzed using Kaplan-Meier estimates (to obtain medians with 95% CI as well as plotting survival curves), log-rank tests, and Cox proportional hazards models. Comparisons between the two treatment arms will be exploratory in nature due to the small sample size. Where applicable, comparisons between groups will be made using a Chi-square test or logistic regression for binary variables and t-tests or analysis of covariance (ANCOVA) or linear regression models for continuous variables. Non-parametric alternatives (e.g. Fisher's exact test or Kruskal-Wallis tests) will be considered as needed as will transformations of the outcome variables (e.g. log).

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).

All statements of statistical significance will be based on a 2-tailed test with an overall 0.05 level of significance, unless stated otherwise. All confidence intervals will be 95%, unless stated otherwise. Sensitivity analyses will include models adjusting for baseline covariables. These

covariates will be selected based upon both clinical significance and potential imbalances between the treatment arms.

Timing of Analysis

The primary analysis will be conducted when all treated subjects have documented response or progression by RECIST 1.1, or have discontinued the study.

13.2 Analysis Sets

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. Since the focus of this study is on establishing the efficacy of the treatment combinations, 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 and therefore focuses upon the effectiveness of the treatment combinations. 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.

13.3 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 CTCAE version 4.03) 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 representing the IND Sponsor. The guidance applies to all immuno-oncology (I-O) agents and regimens.

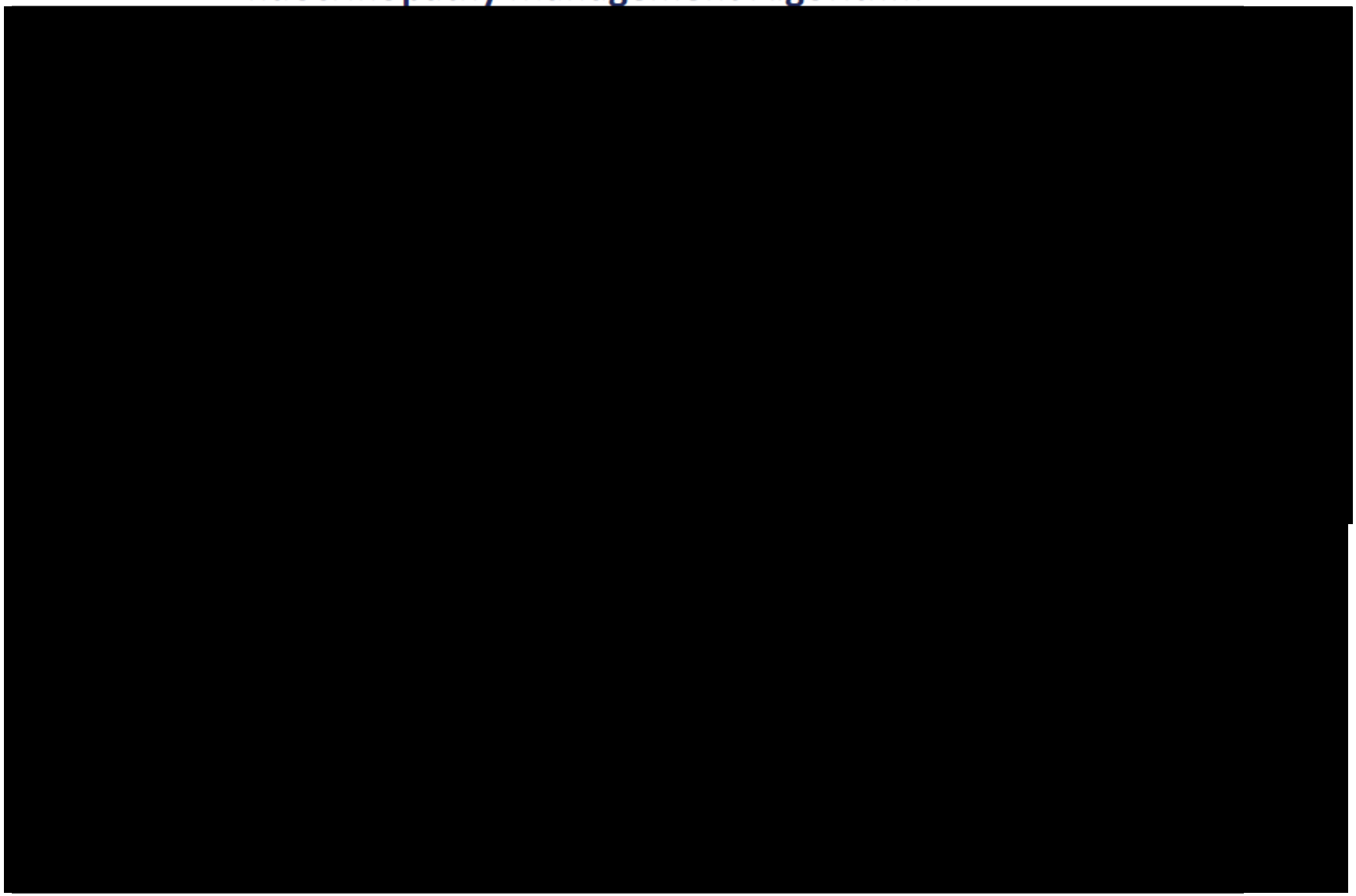
A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

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.

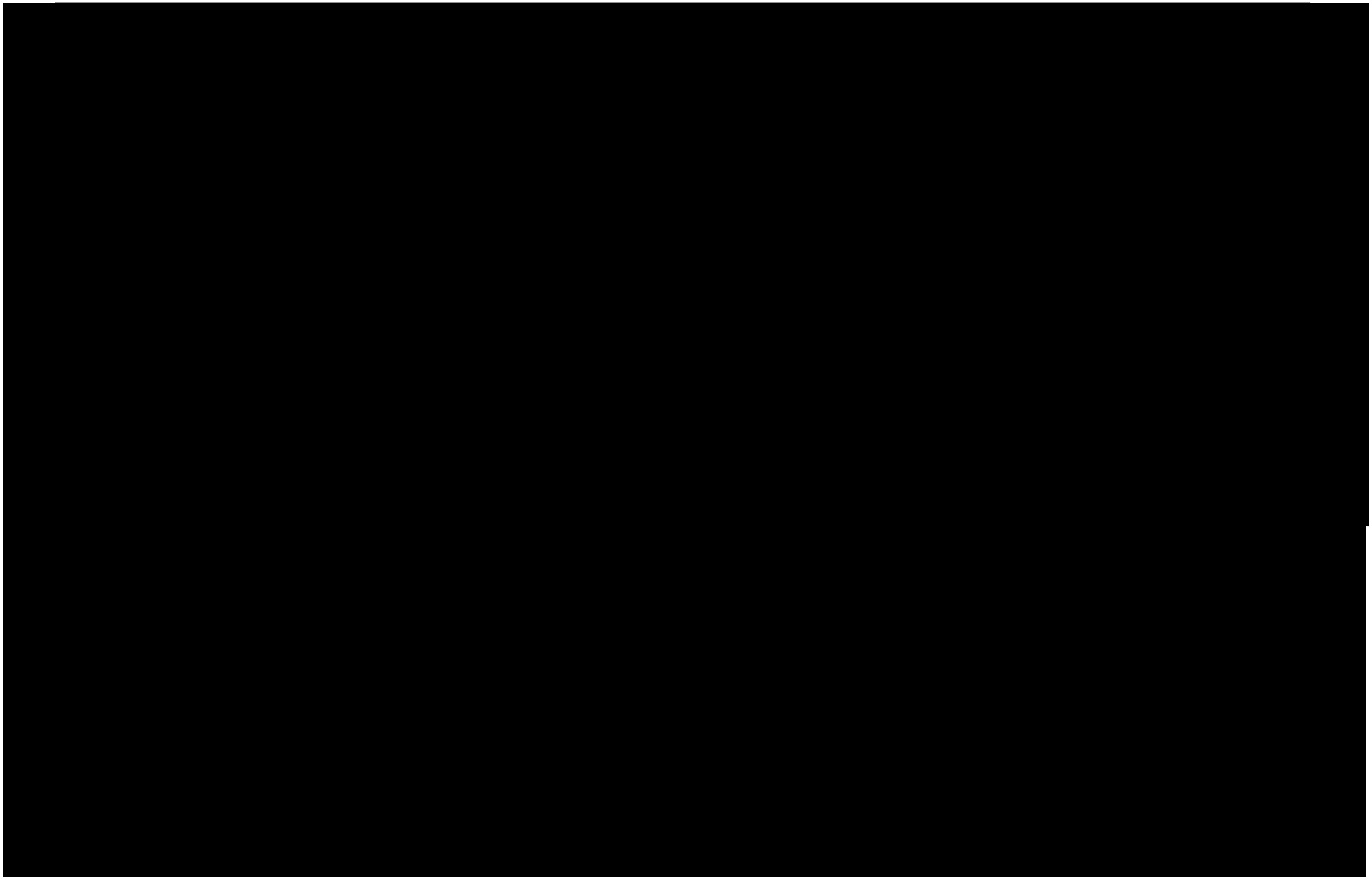
Endocrinopathy Management Algorithm



GI Adverse Event Management Algorithm

Hepatic Adverse Event Management Algorithm

Neurological Adverse Event Management Algorithm



Pulmonary Adverse Event Management Algorithm

Renal Adverse Event Management Algorithm

Skin Adverse Event Management Algorithm

Myocarditis Adverse Event Management Algorithm

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.

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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
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.