Cover Page for Protocol – J16173

NCT Number:	NCT03006302
Official Title of Study	**A Phase 2 Study of Epacadostat, Pembrolizumab, and CRS-207, with or without Cyclophosphamide and GVAX Pancreas Vaccine in Patients with Metastatic Pancreatic Cancer**
Document Date:	April 20, 2021

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Johns Hopkins Protocol #: J16173, IRB00118520

Merck Protocol #: 3475-520

Incyte Protocol #: I-24630-16-06

Principal Investigator: Dr. Dung Le (Protocol Chair)

[redacted]

Co-Investigator: Dr. Katherine Bever

IND Sponsor:

[redacted]

IND: BB IND 16147

Merck Supplied Agent: Pembrolizumab (MK-3475; anti-PD-1 mAb)
Incyte Supplied Agent: Epacadostat (INCB024360)
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®)

Date of Issue:
Version 1.1 / December 14, 2016
Version 1.2 / January 18, 2017
Version 1.3 / March 3, 2017
Version 2.0 / November 29, 2018
Version 3.0 / May 31, 2019
Version 4.0 / June 17, 2020
Version 5.0/ June 25, 2020
Version 6.0/ December 10, 2020
Version 7.0/ April 20, 2021

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1.1 Primary Objectives

1.1.1 The primary objective of Part 1/1X of this study is to determine the recommended dose of epacadostat, in combination with pembrolizumab, CRS-207, cyclophosphamide (CY), and GVAX pancreas vaccine in Part 1, and in combination with pembrolizumab and CRS-207 only in Part 1X.

1.1.2 The primary objective in Part 2X of this study is to determine the 6 month survival rate in previously treated metastatic pancreatic cancer patients receiving epacadostat, pembrolizumab, and CRS-207.

1.2 Secondary Objective

1.2.1 To assess safety and characterize toxicities of anti-programmed death-1 (PD-1), indoleamine 2,3-dioxygenase 1 (IDO1) blockade, and CRS-207 with or without CY/GVAX pancreas vaccine.

1.3 Exploratory Objectives

1.3.1 To assess overall survival (OS), progression-free survival (PFS), objective response rate (ORR), best overall response (BOR), duration of response (DOR), duration of clinical benefit (DCB), time to objective response (TTOR), and disease control rate (DCR) per RECIST 1.1, as well as by immune related response criteria (irPFS, irORR, irBOR, irDOR, irDCB, irTTOR, irDCR).

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

1.3.3 To collect baseline and longitudinal peripheral blood mononuclear cells (PBMC), plasma, and serum to identify potential therapeutic targets, biomarkers, and predictors of response and autoimmune toxicity.

- Measure post-treatment cellular changes in PBMCs including effector, helper, and regulatory T cells, NK cells, monocytes, and macrophages through flow cytometry (FACS) and gene expression profiling.
- Correlate induction of *Listeria monocytogenes* (*Lm*)-specific and mesothelin antigen-specific T cell responses and changes to the T cell receptor repertoire with response assessments.

1.3.4 To collect archived tissue and pre- and on-treatment biopsies to test for predictors of response (OS, PFS and BOR) and future targets for combinatorial therapy.

- Immunohistochemistry (IHC) and/or gene expression profiling will be used to compare the nature of tumors and immune infiltrates for responders versus non-responders.

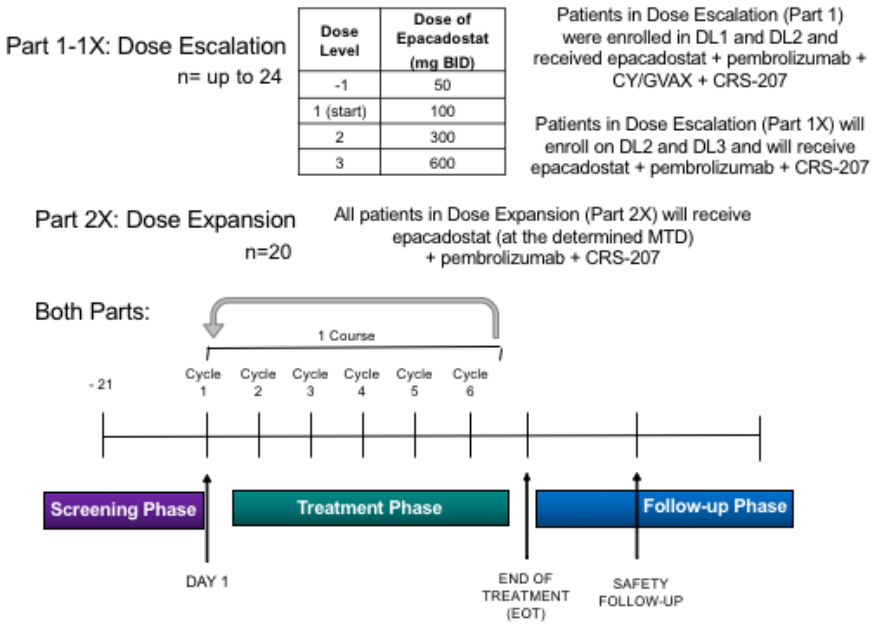
- Up-regulation of immune inhibitory molecules (such as programmed death-ligand 1 [PD-L1] and IDO1) will be evaluated in the pre- and on-treatment samples.
- RNA expression and proteomic analysis to quantify expression and activation of specific signaling pathways in tumors from responders versus non-responders
- TCR repertoire analysis pre and on-treatment

1.3.5 To collect stool and oral wash samples pre- and on-treatment to identify candidate gut microbial biomarkers and predictors of response (OS, PFS and BOR)

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

1.3.6 To explore the effects of therapy on tumor and peripheral blood and tumor infiltrating immune cells, and to explore potential molecular determinants of response, progression and disease stability.

1.4 Study Design



This is an open-label, phase 2 study consisting of 2 parts. Part 1 consists of a 3+3 dose escalation design to determine the dose of epacadostat for use in combination with pembrolizumab, CY/GVAX Pancreas Vaccine, and CRS-207. In Part 1X, patients will continue dose escalation

and will receive epacadostat, pembrolizumab and CRS-207 only. Enrollment will be staggered by at least 1 week for patients enrolled on dose level 3 in Part 1X. The doses of pembrolizumab, CY, GVAX, and CRS-207 are fixed (**Table 3**). Dose limiting toxicities (DLTs) will be assessed through Cycle 4 Day 1 in Part 1, and through Cycle 2 Day 1 in Part 1X. Complete information on the definition of DLTs and dose escalation rules can be found in **Section 4.1**. Treatment in Part 2X will be initiated once the maximum tolerated dose (MTD) for Part 1X has been determined. This will be the dose used in Part 2X.

Part 2X consists of a dose expansion cohort to evaluate the safety and clinical activity of previously treated metastatic pancreatic cancer patients who receive epacadostat, pembrolizumab, and CRS-207. Approximately 20 evaluable patients will be treated (for a total of 26 evaluable patients in Part 2X, including the 6 patients who are treated at the same dose level in Part 1X). Clinical activity will be evaluated in comparison to historical controls, with a 25% 6 month survival being used as the benchmark[1].

For all patients, the study will consist of a screening period, a treatment period, and a follow-up period. Screening evaluations will be done within 21 days prior to start of treatment. Each cycle will be 3 weeks. Each course of treatment will be 6 cycles and courses can be repeated.

Treatment in Part 1 consisted of 2 cycles of pembrolizumab, CY/GVAX pancreas vaccine and epacadostat, followed by 4 cycles of pembrolizumab, CRS-207 and epacadostat. In Part 1X and Part 2X, treatment will consist of 6 cycles of pembrolizumab, CRS-207 and epacadostat. Complete information on study drug administration, schedule, and dosing can be found in **Section 4.3.**

It is estimated that 5% of the subjects who complete screening will not receive study treatment, so approximately 46 subjects are expected to be enrolled to achieve up to 44 treated subjects (up to 24 on Part 1/1X and 20 on Part 2X of the study). 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 in Part 2X with unacceptable toxicity will be monitored routinely using a Bayesian stopping guideline (**Section 12.5**). Complete unacceptable toxicity criteria can be found in **Section 4.9**.

Clinical and immune responses will be evaluated at baseline and during treatment through tumor biopsies, PBMC, serum, and plasma collection, and computed tomography (CT) scans or magnetic resonance imaging (MRI), if CT is contraindicated. Tumor assessments will be made using RECIST 1.1 and irRC.

At the investigator's discretion, subjects may receive additional courses of the assigned treatment regimen if they are clinically stable and meet dosing eligibility criteria. All subjects may continue in the treatment period 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 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 4.12**. To eliminate any potentially residual CRS-207, subjects will initiate a 7-day course of antibiotics 7 days after the subject's last CRS-207 and prior to receiving any subsequent cancer-related therapy (or if the patient will be having a semi-permanent indwelling device placed while on study) per **Section 4.7**. 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 for up to 1 year post-treatment per **Section 4.15**.

Subjects will return to the study site 28 days after the final administration of study treatment for an end-of-treatment (EOT) evaluations and AE assessments. 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. Subjects will also be contacted 90 days from the last dose of pembrolizumab for safety follow-up. Complete information on safety reporting can be found in **Section 7**. After completion of treatment and EOT assessments, all subjects, including those who did not receive treatment, will continue to be followed every 12 weeks by telephone, e-mail, or optional clinic visit until death, withdrawal of consent, or closure of study. Information on survival and new cancer therapies will be collected. Subjects who discontinue treatment for reasons other than disease progression will also continue to be monitored by radiologic imaging every 12 weeks until start of a new anti-cancer therapy, disease progression, death, withdrawal of consent, or the close of the study, whichever occurs first.

The study will be not be closed until all subjects have been followed for at least 12 months from first treatment and the primary analysis timing criteria have been met, or when all subjects have withdrawn from study. Patients will continue to be followed after study closure for survival data. The primary analysis will be conducted when the first of the following has occurred: 6 month survival data is available for the last enrolled and treated subject, or study is closed by sponsor. At the conclusion of the study, all remaining subjects will be offered enrollment in a long-term follow-up study and continue to be followed for survival and clinical and immunological responses.

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[2]. Worldwide it will claim more than 300,000 lives this year[3]. It is projected that by 2030, pancreatic cancer will become the second leading cause of cancer-related death in the US[4].

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)[5]. 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[6]. 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[7]. 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, $p < 0.0001$)[8]. 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[9]. 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 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. IDO1 inhibition in combination with PD-1 targeting is currently under evaluation in clinical trials. PD-1 and IDO1 inhibition have been combined with vaccines in preclinical models as well. Furthermore, PD-1 inhibition with pancreatic cancer vaccines is currently being studied using nivolumab (anti-PD-1) with GVAX Pancreas (allogeneic pancreatic cancer cells modified to express GM-CSF) and CRS-207 (attenuated *Lm* expressing the tumor associated antigen mesothelin).

Pancreatic cancer has been refractory to immunotherapy and a doublet or triplet approach 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

GVAX Pancreas has been combined with immune-modulatory doses of CY to target regulatory T cells (Tregs) and CRS-207 is a live, attenuated, double-deleted *Lm* engineered to secrete mesothelin, a tumor-associated antigen which is overexpressed in most pancreatic cancers, into infected antigen presenting cells, facilitating its presentation in the context of major histocompatibility complexes. GVAX Pancreas and CRS-207 were found to work synergistically in preclinical models and a heterologous prime boost strategy using CY/GVAX Pancreas as a prime and CRS-207 as a boost vaccine has shown, in one study, to provide a survival benefit in patients with metastatic pancreatic cancer with an acceptable safety profile compared to CY/GVAX Pancreas alone[10]. The most frequent grade 3 to 4 related toxicities were transient fevers, lymphopenia, elevated liver enzymes, and fatigue. [redacted] GVAX Pancreas has also been combined with ipilimumab resulting in delayed responses and prolonged survival in a subset of patients[11]. [redacted] A multipronged approach with vaccines and targeting the inhibitory tumor microenvironment is likely necessary in this stromal rich cancer.

IDO and Pancreatic Cancer

IDO is found in pancreatic cancer cell lines[12] and IDO inhibition shows activity in a PANC02 mouse tumor model[13]. In a study of resected pancreatic cancer specimens, IDO expression was associated with an increase in Tregs and was upregulated in the metastases compared to the primary[14]. These authors also showed upregulation of IDO in pancreatic cancer cell lines with IFNγ which would suggest the possibility of IDO as a suppressive mechanism in the microenvironment even with an inflammatory infiltrate. In an analysis of intraductal papillary mucinous neoplasms (IPMN) and pancreatic tumors, high IDO expression was positively correlated with tumor size, TNM stage and tumor markers and high IDO status corresponded with high Treg level as well[15]. These data support IDO as being a promising target for pancreatic cancer.

IDO Inhibition, Immune Checkpoint Blockade, & Vaccines

The inhibition of IDO has been combined with immune checkpoint blockade to enhance treatment effects in difficult tumor models[16,17]. Holmgaard et al demonstrated that IDO-deficient mice had better tumor control than their wild type counterparts when treated with anti-CTLA-4 or anti-PD-1/anti-PDL-1. They were also able to demonstrate efficacy of the combination of anti-CTLA-4 and 1-MT (an IDO inhibitor). Importantly, adding a B16 equivalent of GVAX promoted rejection of 45% of tumors in a difficult tumor model. 1-MT has also been shown to decrease Tregs and slow PANC02 tumor growth in combination with tumor lysate pulsed dendritic cells.

[redacted]

Pembrolizumab

Pembrolizumab is a selective humanized monoclonal antibody of the IgG4/kappa subclass designed to block the interaction between PD-1 and its ligands. It has recently been approved in the United States for the treatment of unresectable or metastatic melanoma, metastatic PD-L1 positive non-small cell lung cancer (NSCLC), and recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) based on tumor response and durability of response[18-21]. [redacted]

Epacadostat

Epacadostat is a selective and reversible oral inhibitor of IDO1, resulting in reduced conversion of tryptophan to kynurenine. An optimal dose of epacadostat for clinical study has not been established; however, higher doses are associated with enhanced enzyme inhibition. When administered at 600mg BID, epacadostat resulted in enzyme inhibition of approximately 90% at steady state, compared to 70% at 300mg BID. Furthermore, in the phase 1 study ECHO-203 of epacadostat plus durvalumab, lower peak exposures were observed in pancreatic cancer patients, suggesting higher doses may be necessary in this group.

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

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

3.1.8 Life expectancy of greater than 3 months.

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

– Leukocytes	≥ 3,000/mcL
– Absolute lymphocyte count	≥ 800/mcL
– Absolute neutrophil count	≥ 1,500/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
– Albumin	≥3.0 g/dL
– Creatinine	≤1.5 × ULN or creatinine clearance (CrCl) ≥ 40 mL/min (if using the Cockcroft-Gault formula below):

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

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

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]). Childbearing potential is defined in Section 4.11.1. 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.

3.1.11 Both women and men of childbearing potential must agree to use adequate method of contraception from the screening visit through 120 days after the last dose of

study treatment. Childbearing potential and methods of contraception are outlined in Section 4.10.1.

3.1.12 All sexually active patients (male and female), must use at least one barrier method of contraception to prevent transfer of body fluids, regardless of other methods or childbearing status.

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

3.2 Exclusion Criteria

3.2.1 Known history or evidence of brain metastases.

3.2.2 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 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 Has received any prophylactic vaccine within 14 days of first dose of study drug (7 days for the COVID vaccine) or received a live vaccine or live-attenuated vaccine within 30 days of study treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, typhoid, and the intranasal flu vaccine.

3.2.7 History of prior treatment with anti-CTLA-4, anti-PD-1, anti-PD-L1, or anti-PD-L2 antibodies or with IDO inhibitor.

3.2.8 Use of 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 Use of UGT1A9 inhibitors or medications that may result in epacadostat metabolite inhibition of CYP1A2, CYP2C8 and CYP2C19, OATP1B1 and OATP1B3 transporters (per **Section 4.6**)

3.2.12 Use of 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.

3.2.13 Known allergy to both penicillin and sulfa.

3.2.14 History of severe hypersensitivity reaction to any monoclonal antibody.

3.2.15 Known or suspected allergy or hypersensitivity to any component of study treatment.

3.2.16 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.

3.2.17 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.

3.2.18 Evidence of clinical ascites. Trace or small amounts of radiographic ascites without prior concern for malignant ascites may be approved by the protocol chair.

3.2.19 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).

3.2.20 New pulmonary embolism, extremity deep venous thromboembolism, or portal vein thrombosis within 2 months of study enrollment (asymptomatic, incidental thrombosis within 2 months of study enrollment may be approved by the Protocol Chair).

3.2.21 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.

3.2.22 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.

3.2.23 Presence of any tissue or organ allograft, regardless of need for immunosuppression, including corneal allograft. Exceptions can be approved by

the Protocol Chair if loss of the graft is not a clinical concern. Patients with a history of allogeneic hematopoietic stem cell transplant will be excluded.

3.2.24 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.

3.2.25 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 undetectable viral load at screening)

3.2.26 Pulse oximetry of < 92% on room air.

3.2.27 Need for supplemental home oxygen.

3.2.28 Unhealed surgical wound or ulcer, or a bone fracture considered non-healing.

3.2.29 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.

3.2.30 Valvular heart disease that requires antibiotic prophylaxis for prevention of endocarditis.

3.2.31 Insufficient peripheral venous access to permit completion of the study dosing and compliance with study phlebotomy regimen

3.2.32 Regular use at the time of consent (including "recreational use") of any illicit drugs or other substance abuse (including alcohol) that could potentially interfere with adherence to study procedures or requirements.

3.2.33 Unwillingness or inability to follow the study schedule for any reason.

3.2.34 Patient is pregnant or breastfeeding.

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

3.2.36 Presence of a gastrointestinal condition that may affect drug absorption.

3.2.37 Use of MAOIs or drug which has significant MAOI activity (meperidine, linezolid, methylene blue) within the 21 days before first dose of study drug. See **Appendix B** for prohibited medications associated with MAO inhibition.

3.2.38 Any history of serotonin syndrome (SS) after receiving serotonergic drugs.

3.2.39 History or presence of an abnormal electrocardiogram (ECG) that, in the investigator's opinion, is clinically meaningful. Screening QTc interval > 480 milliseconds is excluded. For subjects with an intraventricular conduction delay (QRS interval > 120 milliseconds), the JTc interval may be used in place of the QTc with sponsor approval. The JTc must be < 340 milliseconds if JTc is used in place of the QTc. Subjects with left bundle branch block are excluded.

3.2.40 History of organ transplant that requires use of immunosuppressive therapy.

3.2.41 Use of warfarin.

3.2.42 Any condition that would jeopardize the safety of the subject or compliance with the protocol.

3.2.43 History of (non-infectious) pneumonitis that required steroids, evidence of interstitial lung disease or active, non-infectious pneumonitis.

3.3 Inclusion of Women and Minorities

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

4. TREATMENT PLAN

4.1 Dose Escalation (Part 1/1X)

Part 1 consists of a 3+3 dose escalation design to determine the dose of epacadostat for use in combination with pembrolizumab, CY/GVAX Pancreas Vaccine, and CRS-207. Dose escalation rules are outlined below. In protocol version 2.0, enrollment will begin on Part 1X, on which subjects will receive escalating doses of epacadostat given in combination with pembrolizumab and CRS-207 only. Subjects on Part 1X will begin enrollment on Dose Level 2 and will follow the dose escalation schema in **Table 1**. The dose levels being evaluated during dose escalation are provided in **Table 5**. Enrollment on the highest dose level (DL 3) will be staggered by at least one week between patients. DLTs will be assessed from the first day of treatment through Cycle 4 Day 1 in Part 1, and through Cycle 2 Day 1 in Part 1X. Dose escalation will be based on the number of patients experiencing a DLT during this DLT evaluation period. Additional patients may be enrolled to account for patients who have disease progression, die, or drop out without receiving at least one dose of CRS-207 or ≥ 80% of the prescribed dose of epacadostat at the level assigned but have not experienced toxicity. Three to six patients may be enrolled in a cohort, unless unacceptable toxicity is encountered in that dose level.

Table 1: Epacadostat Dose Escalation Guidance

Number of Patients with DLT at a Give Dose Level	Dose Escalation Decision Rule
0 out of 3	Enter 3 patients at the next higher dose level
1 out of 3	Enter 3 more patients at this dose level • If ≤ 1 of 6 subjects in this cohort experience a DLT, proceed to the next higher dose level • If ≥ 2 of 6 subjects in this cohort experience a DLT, this dose level exceeded the MTD and dose escalation will be stopped. 3 subjects will be entered at the next lower dose level.
≥ 2 out of 3 or 6	This dose level exceeded the MTD and dose escalation will be stopped. 3 additional patients will be entered at the next lower dose level.
≤ 1 of 6 (and the next higher level has exceeded the MTD)	This is the MTD. At least 6 patients must be entered at the MTD level to determine the dose to be used in Part 2X of this study.

Individual subject dose reductions of epacadostat may be made based on events observed at any time during treatment; however, for the purposes of dose cohort escalation/de-escalation, expanding a dose cohort, and determining the optimal dose of epacadostat, decisions will be made based on events that are observed from the first day of study drug administration through the DLT evaluation period. A lower dose may subsequently be chosen based on relevant toxicities that become evident after the DLT period.

4.1.1 Dose-Limiting Toxicities

Criteria for determining DLT will be defined the same as for Unacceptable Toxicity (**Section 4.9**) but limited to occurrence through the Cycle 4, day 1 evaluation in Part 1 and through the Cycle 2 Day 1 evaluation in Part 1X. Any toxicity requiring a dose reduction of epacadostat that occurs through Cycle 4 Day 1 in Part 1 or Cycle 2 Day 1 in Part 1X will also be considered as a DLT. Subjects that have had an epacadostat dose-reduction may continue on study at the lower dose once the toxicity resolves to a treatable grade (see **Section 5.2** for dose delay and restart criteria). Subjects that have experienced an unacceptable toxicity will be permanently discontinued from treatment.

All DLTs will be assessed by the investigator using CTCAE v4.03 criteria.

4.1.2 Management and Follow-Up of Dose-Limiting Toxicities

Investigators may employ any measures or concomitant medications necessary to optimally treat the subject.

Any DLT should be followed until it resolves to baseline or appears to have stabilized. During follow-up, subjects should be seen as often as medically indicated to assure safety.

4.2 Dose Expansion (Part 2X)

Part 2X consists of a dose expansion cohort with 26 evaluable patients (including the 6 patients who are treated at the same dose level in Part 1X). Treatment in Part 2X will be initiated once the recommended dose for expansion has been determined from Part 1X.

All patients will receive epacadostat, pembrolizumab, and CRS-207.

4.3 Agent Administration

Treatment will be administered on an outpatient basis. Dosing delays are described in **Sections 4.4 and 5**. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the subject's malignancy.

Subjects will receive treatment every 3 weeks for 6 cycles of treatment within a course. A course of treatment will be 6 cycles (18 weeks). At the investigator's discretion, all subjects may receive additional courses of the assigned treatment regimen up to a maximum of 2 years if they are clinically stable and meet dosing eligibility criteria. Subjects that begin a new course prior to the 2 year cut-off may complete that course prior to coming off study.

Table 2: Treatment Schedule

TREATMENT SCHEDULE						
	Epacadostat	***CY***	***Pembrolizumab***	***GVAX***	***CRS-207***	***Course Length***
Part 1	BID Cycles 1-6	Day 1 Cycles 1, 2	Day 1 Cycles 1-6	Day 2 Cycles 1, 2	Day 2 Cycles 3 -6	18 weeks (6 cycles)
Part 1X/2X	BID Cycles 1-6	-	Day 1 Cycles 1-6	-	Day 2 Cycles 1-6	

Table 3: Regimen Description

REGIMEN DESCRIPTION			
Agent	***Supportive Medications; Precautions***	***Dose***	***Route***
Epacadostat	No premedication; taken Q12h without regard to food	100, 300, 400, or 600 mg	Oral
CY	Subjects may be pre-medicated with anti-emetics prior to CY administration.	200 mg/m^2	IV infusion over 30 min*

REGIMEN DESCRIPTION			
Agent	***Supportive Medications; Precautions***	***Dose***	***Route***
Pembrolizumab	No prophylactic premedication will be given unless indicated by previous experience in an individual subject per **Table 4**	200 mg	IV over 30 minutes*
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)	1×10^9CFU	IV infusion over 1 hour**

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

See **Section 5.1** for information regarding dose reductions. See **Section 5.2** for dosing delay guidelines. 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 documentation and permission from the Protocol Chair needs to be obtained prior to continuation with the other study drugs.

4.3.1 Epacadostat

[redacted]

4.3.1.1 Compliance with Epacadostat

[redacted]

4.3.2 Cyclophosphamide (CY)

[redacted]

4.3.3 Pembrolizumab

[redacted]

4.3.4 GVAX Pancreas Vaccine

[redacted]

4.3.5 CRS-207

[redacted]

4.4 Dosing Criteria

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

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

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

4.5 General Concomitant Medication and Supportive Care Guidelines

4.5.1 Epacadostat

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

4.5.2 Cyclophosphamide (CY)

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

4.5.3 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.

4.5.4 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.

Any 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. Some expected grade 3 or greater laboratory abnormalities such as AST/ALT or bilirubin elevation should also be closely monitored for resolution as clinically indicated.

4.5.5 Pembrolizumab

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

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

4.5.5.1 Infusion Reactions

Pembrolizumab infusion reactions may consist of fever, chills/rigor, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness or hypertension. Severe reactions may include acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. Patients should be closely monitored for such reactions. Guidelines for patients who experience an infusion related or allergic reaction during or after infusion with pembrolizumab are shown in the table below.

Table 4: Pembrolizumab Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids, Antihistamines, NSAIDS, Acetaminophen, Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further pembrolizumab administration.**	Subject may be premedicated 1h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids, Antihistamines, NSAIDS, Acetaminophen, Narcotics, Oxygen, Pressors, Corticosteroids, Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further pembrolizumab administration.**	No subsequent dosing
• Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration. • May use institutional guidelines for management of infusion related reactions		

Refer to **Section 5.2** for guidelines regarding GVAX and CRS-207 treatment delays following a pembrolizumab infusion-related reaction.

4.5.5.2 Immune Related Adverse Events

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). Refer to **Section 5.2** for dose modification. It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

- **Pneumonitis**:
  - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
  - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.

- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

- **Diarrhea/Colitis**:
  Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).
  - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
  - For **Grade 2 diarrhea/colitis,** administer oral corticosteroids.
  - For **Grade 3 or 4 diarrhea/colitis,** treat with intravenous steroids followed by high dose oral steroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
  - For **T1DM** or **Grade 3-4** Hyperglycemia
    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
    - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- **Hypophysitis**:
  - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hyperthyroidism or Hypothyroidism**:
  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
  - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.

        - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care.
    - **Grade 3-4** hyperthyroidism
        - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hepatic**:
    - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
        - Treat with IV or oral corticosteroids
    - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
    - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.
    - Transient Grade 3-4 events are expected immediately after each CRS-207 infusion. Steroid treatment is not indicated for transient elevations.

- **Renal Failure or Nephritis**:
    - For **Grade 2** events, treat with corticosteroids.
    - For **Grade 3-4** events, treat with systemic corticosteroids.
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Myocarditis**
    - For events of **any grade**, treat with corticosteroids as appropriate based on severity
    - Ensure adequate evaluation to confirm etiology and/or exclude other causes

4.6 Prohibited and/or Restricted Medications and Treatments

The following therapies are not permitted during the treatment period:

- Any non-study anticancer chemotherapy or immunotherapy (approved or investigational)
- TNF pathway inhibitors or PI3 kinase inhibitors
- Any other investigational agent
- Any other immunosuppressive-based treatment (see exception for steroid treatment below)
- Use of any MAOI or drug associated with significant MAOI activity agents is prohibited from 21 days prior to first dose through 2 weeks after the final dose of epacadostat has been administered. See **Appendix B** for list of prohibited MAOI-associated agents.
- 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.
- Chronic use of systemic antibiotics (> 14 days) unless approved by the Principal Investigator.
- Use of any UGT1A9 inhibitors including: acitretin, amitriptyline, androsterone, cyclosporine, dasatinib, diclofenac, diflunisal, efavirenz, erlotinib, flutamide, gefitinib, gemfibrozil, glycyrrhetinic acid glycyrrhizin, imatinib, imipramine, ketoconazole (systemic), mycophenolic acid, niflumic acid, nilotinib, phenobarbital, phenylbutazone, phenytoin, probenecid, quinidine, ritonavir, sorafenib, sulfinpyrazone, valproic acid, and verapamil.
- The following medications will be prohibited for concomitant use due to the potential concern for epacadostat metabolite inhibition of CYP1A2, CYP2C8 and CYP2C19, OATP1B1 and OATP1B3 transporters with doses of epacadostat greater than 300 mg BID:

OATP1B1 & 1B3 Transporters	**CYP1A2 Substrates**	**CYP2C8 Substrates**	**CYP2C19 Substrates**
atorvastatin bosentan cerivastatin danoprevir docetaxel[b] fexofenadine glyburide nateglinide paclitaxel[b] repaglinide pitavastatin pravastatin rosuvastatin simvastatin acid fimasartan glecaprevir maraviroc tacrolimus voxilaprevir	**Sensitive:** alosetron caffeine[a] duloxetine melatonin pirfenidone ramelteon selegiline tacrine tasimelteon theophylline tizanidine	**Sensitive:** repaglinide daprodustat dasabuvir montelukast pioglitazone rosiglitazone	**Sensitive:** s-mephenytoin lansoprazole omeprazole tilidine pantoprazole hexobarbital diazepam gliclazide rabeprazole voriconazole proguanil

[a]An epacadostat metabolite is a moderate in vitro inhibitor of CYP1A2, thus it is recommended to avoid or limit caffeine consumption (e.g., no more than 1 cup of coffee or 2-3 soft drinks per day)

[b]Docetaxel and paclitaxel as part of combination therapy with epacadostat at doses < 600 mg BID are permitted.

- Warfarin use is not allowed. The use of anticoagulants is known to increase the risk of gastrointestinal hemorrhage. Since gastrointestinal hemorrhage is an adverse reaction with pembrolizumab, 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 are required to discontinue treatment with CRS-207, but may resume treatment with other study drugs if on ≤10 mg daily prednisone equivalent (in the absence of active autoimmune disease) and if approved by the Protocol Chair or the IND Sponsor.
- If steroids or immunosuppressive agents are required during treatment, prophylactic antibiotics will be administered as outlined in **Section 4.7.**

In addition, the following therapies should not be administered during the treatment period unless medically necessary. Approval must be obtained from the Protocol Chair or IND Sponsor for a subject to continue dosing if any of the following 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)
- More than 2 g/day of acetaminophen
- Systemic antibiotics

4.7 Antibiotic Regimen for Semi-Permanent Indwelling Device Placement

An antibiotic regimen should be initiated for any patient that is having a semi-permanent indwelling device placed such as biliary stents/drains, vascular devices, and pleuryx catheters. If possible, it is recommended that patients receive a dose of Ampicillin/Sulbactam (Unasyn, 3g) with Gentamicin (3 mg/kg) pre-operatively. This should be followed by 8-hour intervals of 1g Amoxicillin (160 mg trimethoprim/800 mg sulfamethoxazole at 12-hour intervals for allergic patients) for 3 days post-operatively.

4.8 Antibiotic Administration after Last CRS-207 Dose in Each Treatment Course, Suspected CRS-207 Infection, or Administration of Steroids or Immunosuppressive Agents for Suspected Treatment-Related AEs

An antibiotic course will be initiated for each subject 7 days after the subject's last dose of CRS-207 for each treatment course or within 7 days of the decision to discontinue treatment if treatment

is discontinued mid-course to ensure clearance of CRS-207 before additional courses or subsequent cancer-related therapy. For subjects who do not have a central line, a 7-day course of oral amoxicillin (1 gram at 8-hour intervals) or trimethoprim/sulfamethoxazole in penicillin-allergic subjects (160 mg trimethoprim/800 mg sulfamethoxazole at 12-hour intervals) will be initiated for each subject. If the patients do not tolerate the 1 gram dose, the antibiotics can be reduced to 500 mg. Subjects with a central line will receive 2 doses [2 g ampicillin 6 hours apart or 3-5 mg/kg trimethoprim/ sulfamethoxazole 8 hours apart (in penicillin-allergic subjects)] of IV antibiotics through the port, followed by 6 days of oral antibiotics [amoxicillin or trimethoprim/sulfamethoxazole (in penicillin-allergic subjects)] started within 6 hours of completeling the IV ampicillin (or within 8 hours from IV trimethoprim/sulfamethoxazole). If the subject is withdrawn from the study more than 7 days after administration of CRS-207, antibiotics will be administered as soon as possible after study withdrawal.

Should a patient require emergent implant of a prohibited device (as described in **Section 4.6**) while on therapy, the patient will receive a 14-day IV antibiotic regimen appropriate for the coverage of wild-type listeriosis.

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

During or after study, subjects who are confirmed to have a blood culture positive for CRS-207 after more than 7 days post-infusion, will receive a minimum 14-day course of IV antibiotics (see below). In addition, IV ampicillin (or trimethoprim/sulfamethoxazole in penicillin-allergic subjects) plus gentamicin should be initiated earlier for possible infectious complications of CRS-207 for subjects who are suspected of having CRS-207 infection and meet the specified criteria (see below).

In the case of suspected persistent CRS-207 infection, blood, urine and stool samples should be obtained in duplicate. One set of samples should be cultured locally for *Lm* 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 *Lm*, the Sponsor must be notified immediately and the duplicate samples sent for testing to confirm CRS-207. Instructions on collection, storage and shipping of samples for CRS-207 testing are provided in the Laboratory Manual.
IV ampicillin (or trimethoprim/sulfamethoxazole in penicillin-allergic subjects) plus gentamicin should be initiated for possible infectious complications of CRS-207 for subjects who are suspected of having CRS-207 infection and meet the criteria listed below:

- Flu-like symptoms Grade 3 or greater lasting for ≥12 hours
- Fever Grade 4 or higher (>40.0ºC for >24 hours)
- Persistent fever >39ºC lasting for ≥48 hours

- Infection Grade 3 or higher (infection with interventional radiology or operative intervention indicated)
- Evidence of abscess
- Clinical signs or symptoms (e.g., neurologic signs or symptoms), which, in the judgment of the investigator, necessitate starting antibiotics

The preferred antibiotic regimen if CRS-207 infection is suspected or confirmed is IV administration of ampicillin (or trimethoprim/sulfamethoxazole in penicillin-allergic subjects) plus gentamicin. For this purpose, initial doses of ampicillin should be approximately 12 g/day (divided doses every 3 to 4 hours), with gentamicin 3 mg/kg daily in divided doses every 8 hours (with adjustments according to renal function and serum levels of gentamicin). In penicillin-allergic subjects, initial IV doses of trimethoprim/sulfamethoxazole should be 15 to 20 mg/kg/day (based on trimethoprim component) divided four times per day, with gentamicin 3 mg/kg/day in divided doses every 8 hours (with adjustments according to renal function and serum levels of gentamicin). For those individuals who receive IV antibiotics, the course of therapy is anticipated to be greater than or equal to 14 days, depending on clinical course. Antibiotic treatment may be completed with use of oral antibiotics, if clinically indicated.

If during the course of treatment the subject develops a reaction to antibiotics such that neither penicillin derivatives nor trimethoprim/sulfamethoxazole can be safely administered, alternative antibiotics such as tetracyclines should be given in all of the above situations. The choice of alternative should be made in discussion with the Protocol Chair, and consultation with infectious disease should be considered.

Follow-up cultures will be obtained periodically to confirm absence/clearance of any CRS-207 infection. The Protocol Chair should be consulted regarding continuation of study drug treatment and treatment of suspected or confirmed infection

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 7.1.4**) 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.

4.9 Definition of an Overdose for this Protocol

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. For pembrolizumab and epacadostat, overdose will be defined as the administration of a dose equal to or greater than 1000mg. All occurrences of overdose must be reported as SAEs (see **Section 7.6.1** for reporting details). Appropriate supportive treatment should be provided if clinically indicated.

All reports of overdose with or without sequelae be reported within 24 hours to the Protocol Chair, IND Sponsor, Merck, and Incyte Corporation (Incyte). Contact information for IND Sponsor, Merck and Incyte can be found in **Section 7.6.1**.

4.10 Unacceptable Toxicity

Unacceptable toxicities are defined as:

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

- 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.

- 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).

- Any toxicity that requires permanent discontinuation per **Table 6** (Dose Delay Guidelines)

- Any treatment-related ≥ grade 3 AE, EXCEPT:
  - Asymptomatic lab 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

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. Any unacceptable toxicity should be followed until it resolves to baseline or appears to have stabilized.

The proportion of unacceptable toxicities will be monitored. If the toxicity levels are unacceptable (>33% of subjects), then enrollment will be suspended until further review and consideration by the Protocol Chair, IND Sponsor, and the Medical Expert Committee (MEC).

See **Section 12.5** for details regarding safety monitoring and stopping rules.

4.11 Contraception, Use in Pregnancy, Use in Nursing

4.11.1 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.

Male subjects will be considered to be of non-childbearing potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female subjects will be considered of non-childbearing potential if they are either:

1. postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.); OR
2. have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening; OR
3. have a congenital or acquired condition that prevents childbearing.

Female and male subjects of childbearing potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:

1. practice abstinence[†] from heterosexual activity; OR
2. use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are:

Single method (must use one of the following):

- Intrauterine device (IUD) or Intrauterine hormone-releasing system (IUS)[†]
- Contraceptive rod implanted in the skin[†]
- Bilateral tubal occlusion or ligation[†]
- Vasectomy of a female subject's male partner[†, ‡]
- Sexual abstinence[¥]

Combination method (must use of two of the following):

- Other hormonal contraceptive:
  - oral contraceptive pill (estrogen/progestin pill or progestin-only pill)
  - contraceptive skin patch
  - vaginal contraceptive ring
  - subcutaneous contraceptive injection
- Diaphragm with spermicide (cannot be used with cervical cap/spermicide)

- Cervical cap with spermicide (nulliparous women only)
- Contraceptive sponge (nulliparous women only)
- Male Condom or female condom (cannot be used together)

† Contraception methods that in the context of this guidance are considered to have low user dependency.

‡ Vasectomised partner is a highly effective method provided of avoiding pregnancy that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.

¥ Abstinence can be used as the sole method of contraception if it is used consistently and is part of your preferred or usual lifestyle. Abstinence during fertile dates (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

4.11.2 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, 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. The outcome of the pregnancy will be reported to the Protocol Chair, IND Sponsor, Incyte, and Merck without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).
The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn. If a male subject impregnates his female partner the study personnel at the site must be informed

immediately and the pregnancy reported and followed as described above and in **Section 7.6.3.**

4.11.3 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.

4.11.4 All Subjects (Male and Female)

All sexually active patients (male and female) must use at least one barrier method of contraception (i.e. condom) to prevent the transfer of body fluids, regardless of other methods of contraception or childbearing status.

4.12 Duration of Therapy

Subjects who are clinically stable and meet dosing requirements (per **Section 4.4**) at the end of the first course may receive additional courses of their assigned treatment based on investigator discretion, 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) will start 3 weeks (+7 days) from last dose of previous course and all assessments will be followed per the study schedule in **Section 9**, 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
- Whole blood for isolation of PBMCs
- Whole blood draw for plasma and serum *Lm*- and mesothelin-specific immunity assays

4.13 Criteria for Removal from Treatment

The reason for study removal and the date the subject was removed will be documented in a CRF.

A subject will be discontinued from study 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 withdraws consent for treatment
- Intercurrent illness that prevents further administration of treatment
- Unacceptable toxicity (see **Section 4.10**) Exceptions may be considered and must be approved by the IND Sponsor if they study treatment has provided clinical benefit (as defined in **Section 4.13.1**).
- Disease progression as defined in **Section 4.13.1 and Appendices C and D**
- Severe or life-threatening study drug-related AE(s) (see **Section 5.2)**
- Need for >2 dose delays due to the same treatment-related toxicity as per the dose delay guidelines (see **Section 5.2**)
- 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

4.13.1 Disease Progression

Epacadostat, GVAX pancreas vaccine, CRS-207, and pembrolizumab 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.

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 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**).

4.14 End of Treatment (EOT)/Safety Follow-up Visit

All subjects will return to the study site approximately 28 days (± 7 days) after the last infusion of study drug (i.e., completion of the final course or upon early discontinuation) for an EOT evaluation. Procedures and assessments performed at these visits and beyond should follow the respective guidelines described in **Sections 4.14 and 9.2** as appropriate.

The EOT visit is conducted only once after the final study treatment. If the EOT visit occurs early (e.g., 1 week prior to the expected visit as protocol allows) or if the patient cannot return due to

disease progression, an assessment for AEs should be made by telephone or email on day 30 (± 1 day) after last dose of study drug and documented.

To eliminate any potentially residual CRS-207, subjects will be administered a 7-day course of antibiotics 7 days after the last CRS-207 dose in each treatment course or after their final dose of CRS-207 if treatment is discontinued early (or if the patient will be having a semi-permanent indwelling device placed per **Section 4.7**. Blood cultures for surveillance of CRS-207 will also be collected per **Section 4.15**.

The subject will be monitored for AEs up to the mandatory EOT/Safety Follow-Up Visit or to resolution of toxicity to ≤ Grade 1, whichever occurs later. SAEs that occur within 90 days (+14 day reporting window) of last dose of pembrolizumab (or for 30 days from the last dose of epacadostat, cyclophosphamide, GVAX, or CRS-207 if the subject is no longer receiving pembrolizumab due to toxicity, whichever reporting period is longer), and before initiation of a new antineoplastic treatment (whichever comes first) should also be followed and recorded.

4.15 Duration of Follow-Up

All enrolled subjects, including those never treated, will enter a follow-up period. Treated subjects will begin the follow-up period after they complete the EOT / Safety Follow-Up Visits. Subjects will be contacted every 12 weeks (and at 90 days [+14 days] from the last dose of pembrolizumab if the subject was still receiving pembrolizumab at the time of treatment discontinuation) to monitor Overall Survival until death, withdrawal of consent, or study closure. Information of other cancer therapies after discontinuation from the study treatment will be collected.

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 12 weeks until, 1) start of a new antineoplastic therapy (information of the new cancer therapy will be collected), 2) documented 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 for at least 4 weeks after their last dose of study drug for the development of AEs. SAEs that occur within 90 days (+14 day reporting window) after the last dose of pembrolizumab or within 30 days (+7 day reporting window) from the last dose of epacadostat cyclophosphamide, GVAX, or CRS-207, if the subject is no longer receiving pembrolizumab due to toxicity (whichever reporting period is longer) should be followed and recorded.

At the conclusion of the study, all remaining subjects who have received at least one dose of study treatment will be offered enrollment in a long-term follow-up study and continue to be evaluated for survival. Subjects who are still receiving treatment at the time of study close may complete the

current treatment course (up to 6 cycles) and EOT/Safety Follow-Up Visit prior to transitioning to participation in the separate long-term follow-up study.

4.16 Blood Cultures for CRS-207 Surveillance

Blood samples from subject's peripheral vein will be obtained at the EOT visit to assess clearance of CRS-207. Subjects who discontinue treatment mid-course should have blood cultures drawn within 4 weeks of the last dose of antibiotics. After EOT, blood will continue to be collected for CRS-207 culture at 3, 6, 9, and 12 months (+/- 1 week window for each collection) for up to 1 year to monitor for the presence of CRS-207. For subjects with a central line, a blood sample will also be taken through the central line at time points indicated for CRS-207 testing. Subjects with samples positive for the presence of CRS-207 will initiate IV antibiotics per **Section 4.7** and be re-tested until negative cultures are confirmed.

4.16.1 Confirmed Listeria Infection

In the event a subject has a positive Listeria culture at any time during or after study participation, the IND Sponsor should be notified within 24 hours of the adverse event of special interest (AESI) per **Section 7.1.4**.

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.

4.16.2 Suspected Infection with CRS-207 or Listeria

In the case of a suspected persistent CRS-207 or Listeria infection that has not been confirmed by culture, collection of blood, urine and stool samples in duplicate is recommended. One set of samples should be cultured locally for Listeria per institutional guidelines. Culture of cerebrospinal fluid should be obtained for subjects with suspected central nervous system infection. In such instances, analysis of cerebrospinal fluid should also include cell count, protein, glucose, and Gram stain. If samples are positive for Listeria, the IND Sponsor 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.

5. DOSING DELAYS, MODIFICATIONS, DISCONTINUATION

5.1 Dose Modifications

Dose reduction or dose increase of CY, GVAX pancreas vaccine, CRS-207 and pembrolizumab will not be permitted. Dose reduction of epacadostat may be permitted after discussion with the Protocol Chair or IND sponsor.

Table 5: Dose Modifications of Epacadostat

Dose Level	Dose of Epacadostat	1st Reduction of Epacadostat	2nd Reduction of Epacadostat
DL -1*	50 mg BID	25 mg BID	-
DL 1	100 mg BID	-	-
DL 2	300 mg BID	100 mg BID	-
DL 3	600 mg BID	400 mg BID	-

*DL -1 will not be explored in Parts 1X/2X

See **Section 4.1** for Dose Limiting Toxicity (DLT) criteria and determination of the Maximum Tolerated Dose (MTD)

See **Section 5.2 and Table 6** for specific epacadostat dose modification criteria.

5.2 Dosing Delays

See **Section 4.4** for dosing parameters. 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 approximately 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 and / or IND Sponsor.

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

- Pembrolizumab-related infusion reactions must resolve to baseline prior to administration of either GVAX or CRS-207.
- Resume Day 2 treatment schedule (GVAX or CRS-207) and assessments without repeating Day 1 study treatments (CY and/or pembrolizumab) if the delay is within 72 hours.
- If the delay is longer than 72 hours, repeat Day 1 and Day 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.

Immune-related adverse events may be attributable to a single agent or a combination of agents. If the event is clearly related to one of the agents, follow the instructions specific for that agent. If the event is related to multiple agents, follow the action taken instructions for each of them.

Epacadostat and pembrolizumab must be withheld for drug-related toxicities per **Table 6** below. See **Section 4.5** for supportive care guidelines, including use of corticosteroids.

Table 6: Pembrolizumab/Epacadostat Dose Modification Guidelines for Related AEs

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Study intervention must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last study intervention treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If study intervention has been withheld, study intervention may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Epacadostat Dose Reduction	Other Criteria for Treatment Discontinuation	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Diarrhea / Colitis	2-3	Toxicity resolves to Grade 0-1	First occurrence: Same dose level Second occurrence: Reduce by 1 level	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/ colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	4 or Recurrent Grade 3	Permanently discontinue	N/A	Permanently discontinue		
AST, ALT Increased	2	Toxicity resolves to Grade 0-1 (see exception below)[b]	First occurrence: Same dose level Second occurrence: Reduce by 1 level	Toxicity does not resolve within 12 weeks of last dose	Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Epacadostat Dose Reduction	Other Criteria for Treatment Discontinuation	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
	3-4	Permanently discontinue. If transient elevation related to CRS-207 (not pembrolizumab or epacadostat), may resume once toxicity resolves to Grade 0-1 at the discretion of the protocol chair (see exception below)[b].	N/A	Permanently discontinue if related to pembrolizumab or epacadostat	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
Increased bilirubin	2	Toxicity resolves to Grade 0-1 (see exception below)[b]	First occurrence: Same dose level Second occurrence: Reduce by 1 level	Toxicity does not resolve within 12 weeks of last dose	Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	3-4	Permanentlly discontinue.	N/A	Permanently discontinue.	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure. Resume when subjects are clinically and metabolically stable.	Same dose level	Resume when patients are clinically and metabolically stable	• Initiate insulin replacement therapy for participants with T1DM • Administer antihyperglycemic in participants with hyperglycemia	Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	2	Once stable on endocrine replacement therapy if patient is asymptomatic.	Same dose level	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks. May also discontinue at the discretion of the investigator for G3-4 events.	Administer corticosteroids and initiate hormonal replacements as clinically indicated	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	3-4	Once stable on endocrine replacement therapy if patient is asymptomatic.				

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Epacadostat Dose Reduction	Other Criteria for Treatment Discontinuation	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hyperthyroidism	3-4	Toxicity resolves to Grade 0-2	Same dose level	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks. May also discontinue at the discretion of the investigator.	Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders
Hypothyroidism	N/A	Therapy can be continued while thyroid replacement therapy is instituted	N/A	Therapy can be continued while thyroid replacement therapy is instituted	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	Monitor for signs and symptoms of thyroid disorders
Infusion Reaction	2[c]	Toxicity resolves to Grade 0-1	N/A	Permanently discontinue if toxicity develops despite adequate premedication	See Section 4.5.5.1	See Section 4.5.5.1
	3-4	Permanently discontinue	N/A	Permanently discontinue		
Pneumonitis	2	Toxicity resolves to Grade 0-1	First occurrence: Same dose level Second occurrence: Reduce by 1 level	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	3-4 or recurrent grade 2	Permanently discontinue	N/A	Permanently discontinue		
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	First occurrence: Same dose level Second occurrence: Reduce by 1 level	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks	Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	Monitor changes of renal function
	3-4	Permanently discontinue	N/A	Permanently discontinue		
Myocarditis	1	Toxicity resolves completely	First occurrence: Same dose level Second occurrence: Reduce by 1 level	Toxicity dose not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	2-4	Permanently discontinue	N/A	Permanently discontinue		

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Epacadostat Dose Reduction	Other Criteria for Treatment Discontinuation	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Neurological Toxicities	Grade 2	Toxicity resolves to Grade 0-1	First occurrence: Same dose level Second occurrence: Reduce by 1 level	Toxicity dose not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue	N/A	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Toxicity resolves to Grade 0-1	First occurrence: Same dose level Second occurrence: Reduce by 1 level	Toxicity dose not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue	N/A	Permanently discontinue		
All Other Drug-Related Toxicities[d]	3 or intolerable/ persistent grade 2	Toxicity resolves to Grade 0-1[e]	Same dose level or reduce by 1 dose level at the discretion of the protocol chair.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks. May also discontinue at discretion of investigator. Guillain-Barre Syndrome and encephalitis require permanent discontinuation.	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	4 or recurrent grade 3	Permanently discontinue (see exceptions below)	N/A	Permanently discontinue		

Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs and is life-threatening event.

[a] Hold Epacadostat for grade 3 or persistent grade 2 diarrhea (grade 2 diarrhea lasting ≥3 days despite symptomatic therapy (i.e. antidiarrheals))

[b] Blood bilirubin > 5 x ULN requires permanent discontinuation. Concurrent blood bilirubin > 2 x ULN **and** AST or ALT > 3 x ULN requires discontinuation.

[c] If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose; Refer to **Table 4** – Infusion Treatment Guidelines for further management details.

[d] Asymptomatic grade 3-4 lab abnormalities do not require dose discontinuation or delay unless specified in **Section 4.4 (Dosing Criteria)**.
Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

[e] Subjects may resume treatment with grade 2 fatigue. Events that require discontinuation include, but are not limited to: encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

Subjects that are required to stop treatment with pembrolizumab and/or epacadostat due to toxicity may stay on study and receive the remainder of the study drugs once the drug-related toxicity(s) has resolved per the restarting criteria in **Table 6** above and only if they are clinically benefiting from the regimen (as per **Section 4.13.1**).

6. PHARMACEUTICALINFORMATION

[redacted]

6.2

[redacted]

[redacted]

6.3

[redacted]

6.4

6.5

[redacted]

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

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

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

All AEs experienced by subjects will be collected and reported from the first dose of the investigational agent, throughout the study, and will be followed for 30 days after last dose of study drug unless related to the investigational agent. All SAEs will be collected and reported through 90 (+14 day reporting window) days following the last dose of pembrolizumab or 30 days (+7 day reporting window) from the last dose of study drug, if the subject is no longer receiving pembrolizumab due to toxicity, whichever reporting period is longer. 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.

Subjects who experience a grade 3 or higher study drug-related AE should be discussed with the Protocol Chair.

7.1 Definitions

7.1.1 Adverse Event

An adverse event (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 grade after starting the study treatment (any procedures specified in the protocol). Conditions that were already present at the time of informed consent and new medical conditions / diseases occurring before starting the study treatment but after signing the informed consent should be recorded on the Medical History CRF and will not be recorded as AEs.

Expected progression of the disease being studied will not be recorded as an adverse event; however, all deaths from time of first administration of study drug through 90 days (+14 day reporting window) after the last dose of pembrolizumab or 30 days (+7 day reporting window) from the last dose of study drug, if the subject is no longer receiving pembrolizumab due to toxicity or before initiation of a new antineoplastic treatment (whichever comes first), regardless of causality or whether subjects have discontinued earlier from treatment, are to be reported as SAEs. Deaths that occur after this reporting window or before initiation of a new antineoplastic treatment (whichever comes first), must be reported as SAEs if they are considered related to study drug.

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. Grade 1 or 2 clinical laboratory abnormalities should be reported as an AE only if they induce clinical signs or symptoms, are considered clinically significant by the investigator, require therapy, or require changes in the study drug(s).

7.1.2 Serious Adverse Event

An 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 or incapacity
- Constitutes a congenital anomaly or birth defect (note: reports of congenital anomalies/birth defects must also be reported on the Pregnancy Form)
- Is another important medical event or medically significant event 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 medical or surgical intervention 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
- **Note:** In addition to the above criteria, adverse events meeting any of the below criteria, although not serious per ICH definition, are reportable in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.
    - 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 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event of Clinical Interest Case Report Form and reported within 24 hours to the IND Sponsor, Incyte, and Merck Global Safety. Events of clinical interest for this trial include:

- An overdose of research product (as defined in **Section 4.8**) that is not associated with clinical symptoms or abnormal laboratory results.
- AST or ALT ≥ 3x the ULN and total bilirubin ≥ 2x ULN and, at the same time, an alkaline phosphatase < 2x ULN

7.1.4 Adverse Events of Special Interest

Suspected infection with CRS-207 and/or Listeria are considered adverse events of special interest (AESI) and should be reported following reporting procedures in **Section 7.6** 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 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.

7.3 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

When the severity of an AE changes over time for a reporting period, each change in severity will be reported as a separate AE until the event resolves.

7.4 Expectedness

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

Expected (known) AE: An AE, which has been reported in the IB, package insert, safety reports or in the Reference Safety Information as applicable. An AE is considered "expected", only if it is included in the IB document as a risk.

7.5 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, package insert, or safety reports), and related to epacadostat, CY, GVAX pancreas vaccine, CRS-207, and/or pembrolizumab. 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.

7.6 Reporting

7.6.1 Adverse Events and Serious Adverse Events

All AEs (both expected and unexpected) will be captured on the appropriate study-specific case report forms (CRFs).

All SAEs and AESI occurring from the first dose of study drug, throughout the study, and 90 days (+14 day reporting window) after the last dose of pembrolizumab or before initiation of a new antineoplastic treatment (whichever comes first) must be reported. All SAEs that the investigator considers related to the study drug occurring after the follow-up periods must be reported.

SAEs will be reported promptly to the IND Sponsor, Merck Global Safety (Merck GS), and Incyte within 24 hours of recognition of the adverse event using the form provided. If this falls on a weekend or holiday, an email notification is acceptable but must be followed by an SAE reporting form on the next business day.

Non-serious Events of Clinical Interest will also be submitted to the IND sponsor, Incyte, and Merck GS within 24 hours using the ECI Reporting Form and will be handled in the same manner as SAEs.

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

Elizabeth Jaffee: [redacted]
Dung Le:
Merck GS:
Incyte:

7.6.2 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. See **Section 7.6.1** for reporting details

7.6.3 Pregnancy Reporting

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report as an SAE any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial or within 120 days following cessation of Sponsor's product. 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 120 days following the male subject's cessation of study drug.

All subjects who become pregnant or partners of subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events) and submitted to the Sponsor, Merck Global Safety, and Incyte. If the pregnancy continues to term, the outcome (health of infant) must also be reported to the Sponsor, Merck Global Safety, and Incyte.

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

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

7.6.5 Food and Drug Administration (FDA)

All reporting to the FDA for the trial will be completed by the IND Sponsor. Each of Merck Global Safety (Merck GS), and Incyte will follow its own standard operating procedures for reporting, if any, to FDA for their respective filings covering the provided investigational products.

7.6.5.1 Expedited IND Safety Reports

7 Calendar-Day Telephone or Fax Report:
The IND Sponsor is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the investigational agent. Such reports are to be telephoned or faxed (301-827-9796) to the FDA within 7 calendar days of first learning of the event. Follow-up information will be submitted to the FDA as soon as relevant information is available.

15 Calendar-Day Written Report:
The IND Sponsor is required to notify the FDA of any SAE that is unexpected and related to the investigational agent in a written IND Safety Report.

Written IND Safety Reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed with the IND concerning similar events should be analyzed. The new report should contain comments on the significance of the new event in light of the previous, similar reports.

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

Investigators will submit a copy of these reports to Merck & Co., Inc, and Incyte Corporation at the time of submission to FDA, using the contact information provided in **Section 7.6.1**

7.6.5.2 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 AEs 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.

7.6.6 Recombinant DNA Advisory Committee (RAC)

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

8. CORRELATIVE / SPECIAL STUDIES

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

8.1 Tumor Tissue Studies

Tumor biopsies (4-6 cores per time point) will be collected at baseline and Cycle 3, only if a subject's tumor is thought to be reasonably safe and easy to biopsy. Fine needle aspiration (FNA)

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 and shipment will be provided in the Laboratory Manual.

To explore the association of OS, PD-L1 positivity, and tumor-infiltrating lymphocyte characteristics with clinical responses, archived tumor tissue and tumor tissue obtained at baseline and during treatment (Cycle 4) will be compared. PD-L1 expression may predict response to anti-PD-1[22,23]. 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 on-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. Evaluation of T cell receptor repertoire and gene expression as well as genomic changes will be conducted on pre and on-treatment biopsy samples. Furthermore, upregulation of other inhibitory molecules such as IL-10 and TGF-β may identify other targets for combinatorial strategies.

8.2 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 reperitoire 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 processing and storage are provided in the Laboratory Manual.

8.3 Serum and Plasma Marker Studies

Sera will be collected prior to dosing on Day 1 of Cycles 1-6 of Course 1 only. Additionally, whole blood for serum will be drawn 20-26 hours post each CRS-207 infusion during Cycles 1-6 of Course 1. Plasma will be collected prior to dosing on Day 1 of Cycles 1, 2, 4, and 6 of Course 1. Humoral immune responses, including anti-*Lm* and anti-mesothelin 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 (-80ºC) until use. Detailed instructions for processing and storage are provided in the Laboratory Manual.

8.4 Stool and Oral Wash Studies

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

Patients will be asked to complete a questionnaire when they provide stool samples, which asks about specific medications, dental health, and diet.

Microbial DNA will be isolated from stool and oral wash samples and prepared for 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, shipment, and storage are provided in the Laboratory Manual.

8.5 Diagnostic Tissue Samples

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

8.6 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.

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.

9. STUDY CALENDAR

Subjects will receive treatment every 3 weeks for 6 cycles of treatment within a course. A course of treatment will be 18 weeks.

9.1 Treatment Part 1

Study Procedures	Screening[21]	Treatment Course (approx. 18 weeks)																					
		Cycle 1[22]			Cycle 2			Cycle 3				Cycle 4				Cycle 5				Cycle 6			
		D1	D2	D8[23]	D1	D2	D8[23]	D1	D2	D3	D9[23]	D1	D2	D3	D9[23]	D1	D2	D3	D9[23]	D1	D2	D3	D9[23]
Visit Windows (days)[1]	D-21 to D1	- 2/ +7	-	±1	- 2/ +7	-	±1	- 2/ +7	-	-	+1	- 2/ +7	-	-	+1	- 2/ +7	-	-	+1	- 2/ +7	-	-	+1
CY		X			X																		
GVAX Pancreas Vaccine			X			X																	
Pembrolizumab[2]		X			X			X				X				X				X			
CRS-207									X				X				X				X		
Epacadostat		X			X			X				X				X				X			
Antibiotics[3]																							X
Informed consent	X																						
Inclusion/exclusion criteria	X																						
Demographics	X																						
Medical-, Cancer-, & Con Med-History[4]	X																						
Con Meds, Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam, ECOG PS[5]	X	X			X			X				X				X				X			
Vitals, Weight, & Height[6]	X	X	X		X	X		X	X			X	X			X	X			X	X		
Hematology, Chemistry[7, 13]	X	X		X	X		X	X		X	X	X		X	X	X		X	X	X		X	X
Endocrine[8, 13]		X			X			X				X				X				X			
Urinalysis[9, 13]	X																						
CD4 count, virology[10]	X																						
Coagulation panel[11]	X																						
Pregnancy Test[12, 13]	X	X			X			X				X				X				X			
CA19-9[13]	X	X			X			X				X				X				X			
ECG[14]	X																						
CT/MRI, RECIST/irRC[15]	X											X											
Vaccine Site Reactions eval.				X			X																

Study Procedures	Screening[21]	Treatment Course (approx. 18 weeks)																					
		Cycle 1[22]			Cycle 2			Cycle 3				Cycle 4				Cycle 5				Cycle 6			
		D1	D2	D8[23]	D1	D2	D8[23]	D1	D2	D3	D9[23]	D1	D2	D3	D9[23]	D1	D2	D3	D9[23]	D1	D2	D3	D9[23]
Whole blood for PBMC[16]		X			X							X								X			
Whole blood for plasma[16]		X			X							X								X			
Serum[16]		X			X			X		X		X		X		X		X		X		X	
HLA[17]		X																					
Stool and Oral Wash Samples[18]	X											X											
Microbiome Questionnaire[18]	X											X											
Archival Tissue[19]	X																						
Tumor Biopsies[20]		X						X															

1: Scheduled cycle may be delayed up to 1 week. Longer delays to be approved by the IND Sponsor, and/or Protocol Chair.

2: Subjects should be observed for a minimum of 30 minutes between CY and pembrolizumab administrations.

3: 7-day course of antibiotics (abx) will be administered 7 days after final dose of CRS-207 in each course (or within 7 days of decision to discontinue treatment if discontinued mid-course) per **Section 4.7**. Subjects with a central line port will receive 1 dose of IV antibiotics followed by 6 days of oral antibiotics; all other subjects will receive 7 days of oral antibiotics. Antibiotic regimens must be completed prior to initiation of any other cancer-related therapy. Abx should also be administered to subjects who receive steroids for the treatment of suspected pembrolizumab-related AE if they have not yet received abx after most recent CRS-207 treatment. Site personnel will contact the subject by telephone to facilitate compliance with antibiotic treatment and document in source.

4: 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.

5: 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.

6: Height will be taken at or prior to screening only. Weight and pulse oximetry will be obtained at screening and prior to each cycle. Blood pressure, pulse, and temperature are required at baseline and as indicated:

CY: vitals will be collected prior to administration.

Pembrolizumab: vitals will be collected prior to and at the end of infusion (-5/+15 minutes).

GVAX pancreas vaccine: vitals will be collected prior to and after administration.

CRS-207: vitals will be obtained 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.

7: Clinical Hematology: CBC with differential ANC, ALC, AEC, monocyte count, and platelet count; Serum Chemistry: sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin, total protein, albumin, calcium, magnesium, and phosphate. Amylase and lipase will be checked only on Day 1 of each cycle. LDH, uric acid, and c reactive protein at baseline only.

8: TSH (total T3 and free T4 only if TSH abnormal as clinically indicated). Prolactin, luteinizing hormone, and ACTH will be done at baseline and repeated only if patient is symptomatic. Cortisol stim test should be considered as clinically indicated if ACTH is abnormal.

9: Color, specific gravity, pH, protein, glucose, ketones, bilirubin, nitrite, blood, leukocytes, WBC and RBC count.

10: Virology screen: HIV antibody, Hepatitis B surface antigen and Hepatitis C antibody; additional virology may also be evaluated.

11: Coagulation panel: D-dimer, fibrinogen, PT, aPTT, and INR

12: 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.

13: Labs may be collected within a window of up to 3 days prior to Day 1 dosing. Blood draws must not be collected from a central line for at least 4 days after infusion of CRS-207. Day 8/9 labs will only be collected during the first course. Any unexpected or clinically significant Grade 3 or greater abnormality should be repeated within 24-72 hours.

14: ECG should be performed at baseline prior to treatment, as clinically indicated while on study, and at the EOT visit.

15: Spiral CT of thorax, abdomen and pelvis (other imaging studies as clinically indicated). If a subject cannot have a CT scan (e.g., allergy to contrast dye), an MRI should be performed. 3-D and RECIST reads will not be used to determine eligibility. 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). EOT scans does 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.

16: Approximately 120 mL of whole blood, 5.0 mL blood for serum, and 20 mL blood for plasma will be drawn as indicated during Course 1 only. Blood may be drawn up to 72 hours prior to Day 1 dosing. Day 3 blood draws (5 mL for serum) should be taken between 20 and 26 hours after start of CRS-207 dosing.

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: Stool and oral wash samples (and questionnaire) will be obtained when available. Specimens should be collected within 72 hours (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 patient has drug-related toxicity or at other timepoints of interest at the discretion of the PI at any point during the trial.

19: Attempts will be made to obtain surgical or biopsy archival tumor samples (other than FNA) for every subject until the sample is obtained or documentation that the sample cannot be obtained is provided. Archived fine needle aspirate (FNA) biopsy samples do not contain sufficient tissue and do not need to be collected.

20: Tumor biopsies (4-6 cores) to be taken at baseline (-1 week) and at Cycle 3 Day 1 (+/- 1 week) of only the first course of treatment. Biopsies will only be collected if subject's tumor is thought to be reasonably safe and easy to biopsy. Additional optional biopsies may be obtained later in the course of study treatment. Fine needle aspiration will not be acceptable. Biopsies will not be collected for patients enrolled in Part 1 of the study (dose escalation).

21: Once a subject meets all eligibility criteria and is randomized/enrolled, the subject does not need to repeat screening evaluations in the event that the first dose is delayed

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

23: Day 8 and 9 assessments may be conducted by phone.

9.2 Treatment Part 1X/Part 2X

Study Procedures	Screening[21]	Treatment Course (approx. 18 weeks)																							
		Cycle 1[22]				Cycle 2				Cycle 3				Cycle 4				Cycle 5				Cycle 6			
		D1	D2	D3	D9[23]	D1	D2	D3	D9[23]	D1	D2	D3	D9[23]	D1	D2	D3	D9[23]	D1	D2	D3	D9[23]	D1	D2	D3	D9[23]
Visit Windows (days)[1]	D-21 to D1	- 2/ +7-	-	-	±1	- 2/ +7	-	-	±1	- 2/ +7	-	-	±1	- 2/ +7	-	-	±1	- 2/ +7	-	-	±1	- 2/ +7	-	-	±1
Pembrolizumab		X				X				X				X				X				X			
CRS-207			X				X				X				X				X				X		
Epacadostat		X				X				X				X				X				X			
Antibiotics[2,3]																									X[24]
Informed consent[25]	X																								
Inclusion/exclusion criteria	X																								
Randomization (R)	X																								
Demographics	X																								
Medical-, Cancer-, & Con Med- History[4]	X																								
Con Meds, Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam, ECOG PS[5]	X	X				X				X				X				X				X			
Vitals, Weight, & Height[6]	X	X	X			X	X			X	X			X	X			X	X			X	X		
Hematology, Chemistry[7, 13]	X	X		X	X	X		X	X	X		X	X	X		X	X	X		X	X	X		X	X
Endocrine[8, 13]		X				X				X				X				X				X			
Urinalysis[9, 13]	X																								
CD4 count, virology[10]	X																								
Coagulation panel[11]	X																								
Pregnancy Test[12, 13]	X	X				X				X				X				X				X			
CA19-9 [13]	X	X				X				X				X				X				X			
ECG[14]	X																								

Study Procedures	Screening[21]	Treatment Course (approx. 18 weeks)																							
		Cycle 1[22]				Cycle 2				Cycle 3				Cycle 4				Cycle 5				Cycle 6			
		D1	D2	D3	D9[23]	D1	D2	D3	D9[23]	D1	D2	D3	D9[23]	D1	D2	D3	D9[23]	D1	D2	D3	D9[23]	D1	D2	D3	D9[23]
CT/MRI, RECIST/irRC[15]	X													X											
Whole blood for PBMC[16]		X				X								X								X			
Whole blood for plasma[16]		X				X								X								X			
Serum[16]		X		X		X		X		X		X		X		X		X		X		X		X	
Microbiome Questionnaire	X													X											
HLA[17]		X																							
Stool and Oral Wash Samples[18]	X													X								X			
Microbiome Questionnaire[18]	X													X								X			
Archival Tissue[19]	X																								
Tumor Biopsies[20]		X								X															

In order to minimize the need for research-only in-person visits, telemedicine visits may be substituted for in person clinical trial visits or portions of clinical trial visits where determined to be appropriate and where determined by the investigator not to increase the participants risks. Prior to initiating telemedicine for study visits the study team will explain to the participant, what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. 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: Scheduled cycle may be delayed up to 1 week. Longer delays to be approved by the IND Sponsor and/or Protocol Chair.
2: 7-day course of antibiotics (abx) will be administered 7 days after final dose of CRS-207 in each course (or within 7 days of decision to discontinue treatment if discontinued mid-course) per **Section 4.8**.
3: Refer to **Section 4.7** for recommended antibiotic regimen for patients having semi-permanent indwelling device placed while on study
4: 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.
5: 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.

6: Height will be taken at or prior to screening only. Weight and pulse oximetry will be obtained at screening and prior to each cycle. Blood pressure, pulse, and temperature are required at baseline and as indicated:

Pembrolizumab: vitals will be collected prior to and at the end of infusion (-5/+15 minutes).

CRS-207: vitals will be obtained 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.

7: Clinical Hematology: CBC with differential ANC, ALC, AEC, monocyte count, and platelet count; Serum Chemistry: sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin, total protein, albumin, calcium, magnesium, and phosphate. Amylase and lipase will be checked only on Day 1 of each cycle. LDH, uric acid, and c reactive protein at baseline only.

8: TSH (total T3 and free T4 only if TSH abnormal as clinically indicated). Prolactin, luteinizing hormone, and ACTH will be done at baseline and PRN. Cortisol stim test should be considered as clinically indicated if ACTH is abnormal.

9: Color, specific gravity, pH, protein, glucose, ketones, bilirubin, nitrite, blood, leukocytes, WBC and RBC count.

10: Virology screen: HIV antibody, Hepatitis B surface antigen and Hepatitis C antibody; additional virology may also be evaluated.

11: Coagulation panel: D-dimer, fibrinogen, PT, aPTT, and INR

12: 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.

13: Labs may be collected within a window of up to 3 days prior to Day 1 dosing. Blood draws must not be collected from a central line for at least 4 days after infusion of CRS-207. Day 8/9 labs will be collected during the first course. Any unexpected or clinically significant Grade 3 or greater abnormality should be repeated within 24-72 hours.

14: ECG should be performed at baseline prior to treatment, as clinically indicated while on study, and at the EOT visit.

15: Spiral CT of thorax, abdomen and pelvis (other imaging studies as clinically indicated). If a subject cannot have a CT scan (e.g., allergy to contrast dye), an MRI should be performed. 3-D and RECIST reads will not be used to determine eligibility. 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). EOT scans does 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.

16: Approximately 120 mL of whole blood, 5.0 mL of blood for serum, and 20 mL blood for plasma will be drawn as indicated during Course 1 only. Blood may be drawn up to 72 hours prior to Day 1 dosing. Day 3 blood draws (5 mL for serum) should be taken between 20 and 26 hours after start of CRS-207 dosing.

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: Stool and oral wash samples (and questionnaire) will be obtained when available. Specimens should be collected within 72 hours (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 patient has drug-related toxicity or at other timepoints of interest at the discretion of the PI at any point during the trial.

19: Attempts will be made to obtain surgical or biopsy archival tumor samples (other than FNA) for every subject until the sample is obtained or documentation that the sample cannot be obtained is provided. Archived fine needle aspirate (FNA) biopsy samples do not contain sufficient tissue and do not need to be collected.

20: Tumor biopsies (4-6 cores) to be taken at baseline (-1 week) and at Cycle 3 Day 1 (+/- 1 week) of only the first course of treatment. Biopsies will only be collected if subject's tumor is thought to be reasonably safe and easy to biopsy. Additional optional biopsies may be obtained later in the course of study treatment. Fine needle aspiration will not be acceptable.

21: Once a subject meets all eligibility criteria and is randomized/enrolled, the subject does not need to repeat screening evaluations in the event that the first dose is delayed

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

23: Day 8 and 9 assessments may be conducted by phone.

24: 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 soruce.

25: 30 day window

9.3 End of Treatment and Follow-Up

Visit Day (Range)	EOT	Follow-Up Phase		Comments
		Safety Follow-Up[i)]	Survival Follow-Up	
	28 Days After last Dose of Study Drug	90 Days After Last Dose of Study Drug	Every 12 Weeks	
Evaluation/Window	**+/- 7 Days**	**+14 Days**	**+/- 2 Weeks**	
Survival Follow-Up			X	Subjects will be assessed by either a clinic visit or phone contact every 12 weeks (+/- 2 wks) from the last dose of study treatment.
Post-Study Anti-Cancer Tx			X	The nature and start and stop dates of any new cancer therapies during follow-up period will be recorded.
Physical Exam, ECOG PS	X			
Vital signs, weight	X			
ECG	X			
Con Meds	X			
Adverse Events	X	X		AEs must be monitored for 30 days after the last dose of study drug; however, SAEs must be monitored up to 90 days.
Laboratory assessments	X			
CT/MRI, RECIST/irRC	X		X	EOT imaging may be done +/- 4 weeks from EOT visit. Subjects discontinuing treatment for reasons other than disease progression, should continue imaging every 12 weeks (+/- 2 weeks) until (1) start of new anticancer therapy, (2) documented disease progression, (3) death, (4) withdrawal of consent or (5) the end of study, whichever occurs first.
Hematology, Chemistry	X			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, total protein, albumin, calcium, magnesium, and phosphate.
Endocrine	X			TSH (total T3 and free T4 if TSH abnormal as clinically indicated). Prolactin, luteinizing hormone, and ACTH if patient is symptomatic. Cortisol stim test only if ACTH abnormal).
Blood sample for CRS-207 testing	X			Blood for CRS-207 culture will be collected at EOT (or within 4 weeks of last dose of antibiotics if patients discontinue treatment mid-course) to assess clearance of CRS-207. After EOT, 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) to monitor for the presence of CRS-207.
Stool and Oral Wash Samples, Microbiome Questionnaire	X			Stool and oral wash samples (and questionnaire) will be obtained when available. Specimens should be collected within 72 hours (ideally within 24 hours) of the patient's appointment.

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

10. STUDY ENDPOINTS

10.1 Primary Endpoint

The primary endpoint is 6 month survival rate, measured from date of first treatment.

10.2 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)
  - Pembrolizumab-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

10.3 Exploratory Endpoints

Exploratory endpoints are as follows:

- Overall Survival (OS), Progression-Free Survival (PFS), Objective Response Rate (ORR), Best Overall Response (BOR), Duration of Response (DOR), Duration of Clinical Benefit (DCB), Time to Objective Response (TTOR), and Disease Control Rate (DCR) measured by RECIST 1.1. The same endpoints will be measured using irRC (irPFS, irORR, irBOR, irDOR, irDCB, irTTOR, irDCR)
  - OS will be measured from date of first treatment 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 first treatment to disease progression (PD or relapse from CR) or death due to any cause.
  - Objective Response Rate (ORR) is defined as the percentage of subjects achieving a partial response or better (PR + CR)
  - Best Overall Response (BOR) is defined in **Appendix C**.

  - Duration of Response (DOR) is defined as the number of months from the first documentation of a response to date of disease progression.
  - Duration of Clinical Benefit (DCB) is defined as the number of months from first treatment to date of disease progression in those achieving a PR or CR.
  - Time to Objective Response (TTOR) is defined as the number of months from the date of first treatment to the date of documented partial or complete response
  - Disease Control Rate (DCR) is defined as the percentage of subjects achieving stable disease or better (SD + PR + CR)
- Tumor marker kinetics measured by change in serum CA19-9 concentrations from baseline
- 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 by FACS in PBMCs including effector, helper, and regulatory T cells, NK cells, and macrophages
- T cell receptor (TCR) repertoire analysis in PBMCs and tumors
- Gene expression analysis of PBMCs
- 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.

11. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event 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.

11.1 Data Management

All information will be collected on study-specific case report forms (CRFs) by study staff. These data will be reviewed for completeness and accuracy by the Principal Investigator.

11.2 Safety Meetings

Scheduled meetings will take place weekly and will include the protocol principal investigator, study coordinator(s), data manager(s), sub-investigators (as appropriate), collaborators (as appropriate), and biostatisticians (as appropriate) involved with the conduct of the protocol. During these meetings matters related to the following will be discussed: safety of protocol participants,

validity and integrity of the data, enrollment rate relative to expectation, characteristics of participants, retention of participants, adherence to protocol (potential or real protocol violations), data completeness, and progress of data for objectives.

11.3 Monitoring

The SKCCC Compliance Monitoring Program will provide external monitoring for JHU affiliated sites in accordance with SKCCC DSMP (Version 6.0, 02/21/2019). The SMC Subcommittee will determine the level of patient safety risk and level/frequency of monitoring. The protocol will be internally monitored by Dr. Dung Le. Additional data and safety monitoring oversight will also be performed by the SKCCC Safety Monitoring Committee (SMC - as defined in the DSMP) and a Medical Expert Committee (MEC) as detailed below.

The Medical Expert Committee (MEC) for this clinical study contains three medical oncologists from other disciplines who are not affiliated with this clinical trial protocol. The MEC will review safety data on at least a semi-annual basis. The MEC will provide a written summary of each assessment to the IND Sponsor-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. STATISTICAL CONSIDERATIONS

12.1 Sample Size

Part 1 of the trial evaluated up to 3 dose levels of epacadostat in combination with pembrolizumab, CY/GVAX pancreas vaccine, and CRS-207 (including dose level -1) using a 3+3 dose escalation approach. Enrollment will continue according to this approach on Part 1X, but with an additional dose level to be evaluated, and patients will receive epacadostat with pembrolizumab and CRS-207 only. Up to 24 patients will be enrolled in Part 1/Part 1X.

For Part 2X, the primary endpoint is 6 month overall survival (6mo OS), and will be calculated as

the proportion of subjects who are alive 6 months or longer after the date of first treatment.

A total of 26 evaluable patients are planned, and will include the 6 subjects from part 1X treated at the same dose. mTOR inhibitor sirolimus showed 26% 6mo OS in gemcitabine-resistant pancreatic cancer[1], and we expect the combination immunotherapy to achieve better efficacy. A sample size of 26 provides greater than 90% power to reject the null hypothesis of 25% 6mo OS rate in favor of 50% 6mo OS, with type I error of 0.1. If 10 or more patients survive beyond 6 months, we conclude that treatment is effective and further study is warranted. No early stopping for futility is planned due to the relatively rapid enrollment of patient in relation to the 6-months OS endpoint. It is estimated that 5% of the subjects who complete screening and are enrolled will ultimately not receive study treatment, so approximately 28 subjects are expected to be enrolled to achieve 26 treated subjects.

12.2 Analysis sets

The Full Analysis Set (FAS) is defined as all subjects who received at least 1 dose of study treatment. The FAS will be used for the analysis of efficacy endpoints.
The Safety Set includes all subjects who received any study treatment. In all safety analyses, the treatment group at analysis will be based on actual treatment received. All analyses of safety data will be conducted using the safety set.

12.3 Statistical Analyses

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

Primary endpoint of 6mo OS will be estimated as the fraction of patients who are alive beyond 180 days after first treatment, with corresponding 95% confidence interval. In the rare event that survival status is not available for one of more subjects, these will be treated as a death event for this endpoint.

Objective response rate (ORR) will be estimated as the proportion of patients who achieve complete response (CR) or partial response (PR) per RECIST 1.1. Time to objective response (TTOR) and duration of response (DOR), defined as time from first treatment to CR/PR and from response to disease progression among responders, respectively, will be summarized. Disease control rate (DCR) is defined as fraction of patients who have CR, PR or stable disease. Time-to-event outcomes such as progression-free survival (PFS) and OS will be analyzed using Kaplan-Meier estimates. PFS is defined as the time from first treatment to the first documented disease progression per RECIST 1.1 or death due to any cause, whichever occurs first, and OS is defined as the time from first treatment to death due to any cause. Those who are lost to follow up will be censored at the last date they were known to be alive. The same analysis will be performed to describe these outcomes based on immune related response criteria (irPFS, irORR, irDOR, irTTOR, irDCR).

For correlative studies, plots will be used to show the changes in immune response over time for each individual. 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 groups for cross-sectional data (e.g., linear and logistic regression) and longitudinally with appropriate correction for correlation between repeated measurements (e.g., linear mixed effects models).

Demographics and baseline characteristics will be summarized.

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

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

12.5 Safety monitoring

The proportion of treated subjects with unacceptable toxicity will be monitored routinely using a Bayesian stopping guideline in Part 2X of the trial. If the unacceptable toxicity events appear to be higher than 33%, we will temporarily halt the study pending further review and consideration. Specifically, we will apply a Bayesian toxicity monitoring rule that suspends the enrollment if the posterior probability of risk being larger than 0.33 is 65% or higher. The monitoring rule uses beta (1.5, 5.5) as prior distribution. This means that our prior guess at the proportion of toxicity is 21%, and there is 90% probability that this proportion is between 3% and 49%. The decision rule for safety stopping among the additional 20 patients enrolled is as follows:

Stop if:

# AE	3	4	5	6	7	8	9
Out of	3-4	5-7	8-10	11-12	13-15	16-18	19-20

For example, if three out of the first 3-4 patients have unacceptable toxicity events, we will stop the accrual. If four or more out of the first 5-7 patients have unacceptable toxicity events, we will stop.

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

True AE rate	% simulated trials declaring unsafe	Average sample size (out of 20)
0.2	7.5	19
0.25	14.9	18.2
0.3	27.6	16.9
0.35	43.4	15.2
0.4	59.4	13.3
0.45	73.3	11.5

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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. Prohibited MAOIs and Drugs Associated with Significant MAOI Activity[1]

Monoamine Oxidase Inhibitors	Drugs Associated With Significant Monoamine Oxidase Inhibitory Activity
Hydrazines (example phenelzine)	Meperidine[2]
Caroxazone	Linezolid
Echinopsidine	Methylene blue
Furazolidone	
Tranylcypromine	
Brofaromine	
Metralindole	
Minaprine	
Moclobemide	
Pirlindole	
Toloxatone	
Lazbemide	
Pargyline	
Rasagiline	
Selegiline	

[1] Review of serotonin syndrome:
Edward W. Boyer, M.D., Ph.D., and Michael Shannon, M.D., M.P.H. The Serotonin Syndrome. *N Engl J Med* **352**:1112-1120, http://www.nejm.org/doi/full/10.1056/NEJMra041867

[2] Up to 2 doses of meperidine may be used for the treatment of rigors during CRS-207 infusion.

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

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

Disease Parameters

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

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

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

> Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
>
> 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

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

further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

Evaluation of Target Lesions

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

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

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

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

Evaluation of Non-Target Lesions

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

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

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

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

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

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease

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

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

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

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

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

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

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

Reference

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

APPENDIX D. Immune-Related Response Criteria

Comparison between RECIST 1.1 criteria and the irRC

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

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

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

Measurable response	Non-measureable response		Overall response
Index and new, measurable lesions; tumor	Non-index lesions	New, non-measurable lesions	Using irRC
↓ 100	Absent	Absent	irCR$^{\pm}$
↓ 100	Stable	Any	irPR$^{\pm}$
↓ 100	Unequivocal progression	Any	irPR$^{\pm}$
↓ ≥ 30	Absent/ Stable	Any	irPR$^{\pm}$
↓ ≥ 30	Unequivocal progression	Any	irPR$^{\pm}$
↓ <30 to <20↑	Absent/ Stable	Any	irSD
↓ <30 to <20↑	Unequivocal progression	Any	irSD
≥ 20↑	Any	Any	irPD$^{\pm}$

*Decreases assessed relative to baseline, including measurable lesions only (>5 x 5 mm).
$^{\pm}$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.