CLINICAL STUDY PROTOCOL

A Phase 1/2, Open-Label Safety and Efficacy Evaluation of CRS-207 in Combination with Epacadostat in Adults with Platinum-Resistant Ovarian, Fallopian, or Peritoneal Cancer

Investigational Products: CRS-207, epacadostat, and pembrolizumab
Protocol Number: ADU-CL-11

Sponsor:
Aduro Biotech, Inc.
740 Heinz Avenue
Berkeley, CA 94710-2224 USA
Telephone: +1 510-848-4400
Facsimile: +1 510-848-5614

Original Protocol: 28 October 2015
Amendment 1: 22 April 2016
Amendment 2: 15 November 2016
Amendment 3: 18 February 2017
IND: 16,702

SIGNATURE PAGE

STUDY TITLE: A Phase 1/2, Open-Label Safety and Efficacy Evaluation of CRS-207 in Combination with Epacadostat in Adults with Platinum-Resistant Ovarian, Fallopian, or Peritoneal Cancer

We, the undersigned, have read this amended protocol and agree that it contains all necessary information required to conduct the study.

Signature	Date
Natalie Sacks	21 Feb 17

Natalie Sacks, MD
Chief Medical Officer
Aduro Biotech, Inc.

Leisha A Emens	02/21/2017

Leisha Emens, MD, PhD
Associate Professor of Oncology
Johns Hopkins University School of Medicine

	02/23/2017

Dirk Brockstedt, PhD
Executive Vice President, Research and Development
Aduro Biotech, Inc.

INVESTIGATOR AGREEMENT

By signing below I agree that:

I have read this amended protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by Aduro Biotech, Inc. to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to Aduro Biotech, Inc. and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by Aduro Biotech, Inc., with or without cause. I have the right to suspend enrollment of subjects at my study site if necessary to protect the best interests of the study subjects.

I agree to conduct this study in full accordance with Food and Drug Administration Regulations, Institutional Review Board/Ethic Committee Regulations and ICH Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

TITLE: A Phase 1/2, Open-Label Safety and Efficacy Evaluation of CRS-207 in Combination with Epacadostat in Adults with Platinum-Resistant Ovarian, Fallopian, or Peritoneal Cancer

PROTOCOL NUMBER: ADU-CL-11

INVESTIGATIONAL PRODUCTS:

CRS-207, epacadostat (IDO), and pembrolizumab (pembro)

OBJECTIVES AND ENDPOINTS:

The objectives and endpoints for this study are as follows:

Phase 1: Dose Evaluation, Assigned Arms

Objective(s)	Endpoints
Primary • Determine the RP2D of epacadostat administered with CRS-207 in subjects with platinum-resistant ovarian, fallopian or peritoneal cancer • Assess safety and tolerability of CRS-207 alone and CRS-207 in combination with epacadostat in subjects with platinum-resistant ovarian, fallopian or peritoneal cancer	**Primary** • Hematologic and non-hematologic DLTs; • Adverse events by CTCAE grade; vital signs, physical exam findings, changes in ECG readings and changes in chemistry and hematology and coagulation parameters

Secondary
• Characterize the PK of epacadostat
• Evaluate the preliminary anti-tumor activity of each study drug regimen
• Characterize pharmacological effects on immune biomarkers in peripheral blood and tumor tissue
• Characterize shedding and clearance of CRS-207 when given alone or with epacadostat
	Secondary
	• Plasma concentration of epacadostat and derived PK parameters;
	• ORR, defined as CR or PR as determined by mRECIST, RECIST v1.1, and GCIG CA-125 criteria;
	• PFS, defined as the time from the date of first dose to PD or death due to any cause. PFS is measured through the last tumor assessment or commencement of a new systemic therapy. PD is determined by mRECIST, RECIST v1.1 and GCIG CA-125 criteria;
	• Disease control rate, defined as CR+PR+SD as determined by mRECIST, RECIST v1.1, and GCIG CA-125 criteria;
	• Duration of response, defined as the time from first CR or PR until PD as determined by mRECIST, RECIST v1.1, and GCIG CA-125 criteria;
	• OS, defined as the time from first dose until date of death due to any cause;
	• Ratio of tumor infiltrating lymphocytes CD8/T_{reg} (FoxP3);
	• Plasma kynurenine/tryptophan ratio;
	• Other immunological and tumor biomarker endpoints:
	  o Cytokine/chemokine responses
	  o Antibody responses
	  o Modulation of immune cell populations and functions in PBMCs and tumor, and
	  o CA-125, mesothelin, IDO-1, PD-L1 and additional tumor biomarkers; and
	• Detection of CRS-207 in urine, saliva, feces, and blood

CA-125 = cancer antigen-125; CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events; DLT = dose-limiting toxicity; GCIG = Gynecologic Cancer Intergroup; IDO = epacadostat; mRECIST = modified Response Evaluation Criteria in Solid Tumors; ORR = objective response rate; OS = overall survival; PBMC = peripheral blood mononuclear cells; PD = disease progression; PD-L1 = programmed death receptor ligand 1; pembro = pembrolizumab; PFS = progression-free survival; PK = pharmacokinetics; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended Phase 2 dose; SD = stable disease; T_{reg} = regulatory T cells.

Phase 2: Randomized, 2-stage

Objective(s)	Endpoints
Primary • Assess safety of CRS-207/pembrolizumab administered with or without epacadostat • Assess tumor response and PFS	**Primary** • Adverse events, vital signs, physical exam findings, changes in ECG readings, and changes in chemistry, hematology, and coagulation parameters • ORR, defined as CR or PR as determined by mRECIST • PFS, defined as the time from the date of first dose to PD or death due to any cause. PFS is measured through the last tumor assessment or commencement of a new systemic therapy. PD is determined by mRECIST.
Secondary • Assess disease control rate and duration of response • Assess OS	**Secondary** • Disease control rate, defined as CR+PR+SD as determined by mRECIST, RECIST v1.1, and GCIG CA-125 criteria • Duration of response, defined as the time from first CR or PR until PD as determined by mRECIST, RECIST v1.1, and GCIG CA-125 criteria • ORR as determined by RECIST v1.1 and GCIG CA-125 criteria • OS, defined as the time from first dose until date of death due to any cause • PFS where PD is determined by RECIST v1.1 and GCIG CA-125 criteria
Additional • Assess the association of clinical efficacy (ORR, PFS, and OS) with immunologic and tumor biomarkers • Characterize the PK of epacadostat • Characterize shedding and clearance of CRS-207/pembrolizumab administered with or without epacadostat	**Additional** Immunological and tumor biomarker endpoints: • Cytokine/chemokine and antibody responses • Modulation of immune cell populations and functions in PBMCs and tumor • Mesothelin, IDO-1 and PD-L1 expression • CA-125 and additional candidate tumor biomarkers Pharmacokinetic endpoints: • Plasma concentration of epacadostat and derived PK parameters • Detection of CRS-207 in urine, saliva, feces, and blood

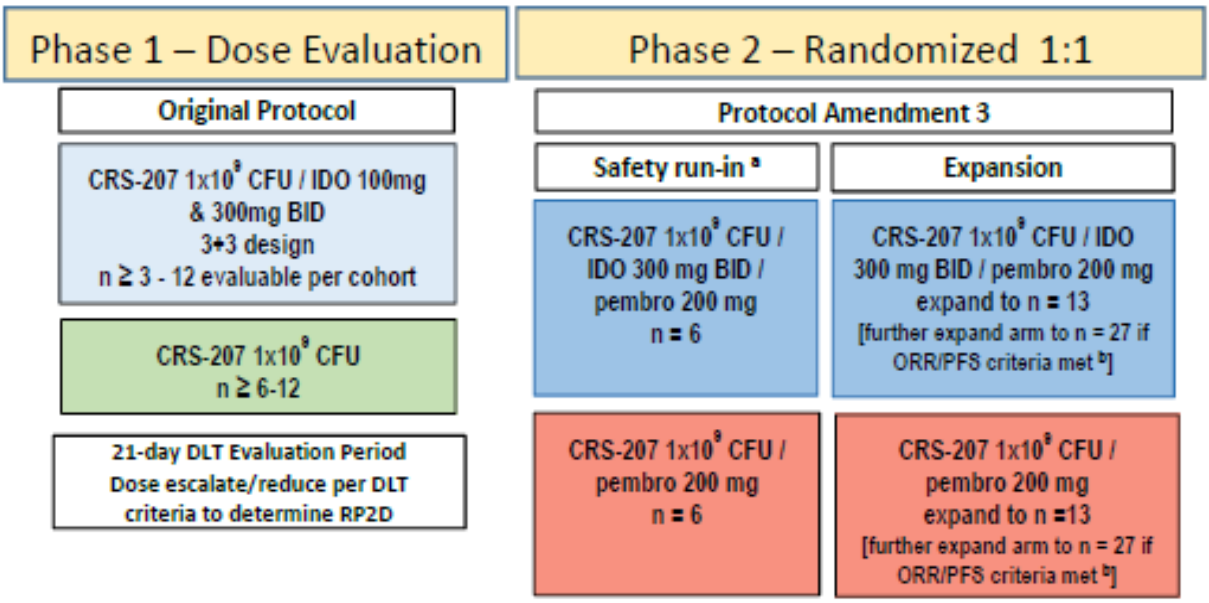
STUDY DESIGN:

The study is designed to assess the safety and efficacy of the following investigational treatment regimens in adult females with epithelial ovarian, fallopian, or primary peritoneal cancer that is platinum-resistant (i.e. has progressed within 6 months after completing platinum-based chemotherapy):

- CRS-207/epacadostat/pembrolizumab (CRS-207/IDO/pembro)
- CRS-207/pembrolizumab (CRS-207/pembro)

The study will be conducted in 2 phases as depicted in the study schematic. Phase 1 seeks to evaluate safety and tolerability and is aimed at determining the recommended Phase 2 dose (RP2D) of epacadostat administered with CRS-207 for further evaluation in Phase 2. The randomized Phase 2 portion of the study will begin with a safety-run in to evaluate the addition of pembrolizumab, followed by a 2-stage design to evaluate safety and efficacy in subjects who have received no more than 3 prior chemotherapy regimens for locally advanced or metastatic disease.

Study Schematic



IDO = epacadostat

[a] A Safety Run-in will be completed at the RP2D for the first 12 randomized subjects (6 per arm). Treatment of the first 6 subjects in each arm will be staggered, with no more than 1 subject treated per arm, per week. Subjects will be monitored during the first 28 days (at least through 7 days after the Cycle 2 pembro/CRS-207 infusions). The SRC will review adverse events on an ongoing basis; in the event 2 or more subjects in the first 6 treated experience DLTs, the SRC will be convened to determine if a dose modification is required. If the phase 2 dose is modified, at least 13 subjects will be enrolled and treated at the final dose level.

[b] If ORR/PFS criteria are met, enrollment in that Arm is continued to n = 27. The ORR/PFS criteria are: Among the first 13 subjects (at the final dose level) ≥1 respond or median PFS ≥ 4.8 months.

The Schedules of Events for Phases 1 and 2 are provided in Appendix F and Table 1, respectively. The study consists of a 28-day screening period, followed by administration of study drug(s) in 3-week cycles. Treatment will continue for as long as there is adequate safety and potential for clinical benefit with the exception that pembrolizumab may be given for up to 24 months to subjects without disease progression. After 6 cycles, CRS-207 will be administered every 6 weeks (Q6W); all other assigned treatments remain the same.

Archived tumor tissue and paired tumor biopsies (collected at Screening and Cycle 2 Day 15) will be used to explore the association of programmed death receptor ligand-1 (PD-L1) expression, mesothelin expression, and tumor-infiltrating lymphocyte (TIL) characteristics with clinical responses. Tumor evaluation by radiographic imaging will be performed within 28 days

prior to treatment and every 9 weeks while on treatment and until disease progression. Peripheral blood will be collected to assess immune responses directed against *L. monocytogenes*, mesothelin, and other tumor-associated antigens. Circulating levels of Cancer antigen 125 (CA-125) will be assessed at Screening and on Day 1 of each 3 week cycle while on treatment, and every 9 weeks thereafter until disease progression is confirmed. CRS-207 shedding and clearance will be assessed during Phase 1 and during the Safety Run-in of Phase 2 at US sites only. Urine, rectal swab, oral swab, and whole blood will be collected from subjects treated with CRS-207. Additional assessments will be performed if results are positive for CRS-207 at the Day 8 time point.

An End-of-Treatment (EOT) Visit will be scheduled once treatment has been discontinued. Blood will be collected at EOT to assess clearance of CRS-207 and at [redacted]. To eliminate any potentially residual CRS-207, subjects will be administered antibiotics at the EOT Visit; the antibiotic regimen should be completed prior to receiving any subsequent cancer-related therapy. An additional Safety Follow-up Visit will occur 30 days after the last dose of study drug. If the subject begins another anticancer therapy before the end of the 30-day period, the subject should complete all of the Safety Follow-up Visit assessments prior to commencing the new therapy.

After the Safety Follow-up Visit, subjects will return to the clinic every 9 weeks for tumor evaluation and CA-125 until radiographic disease progression is confirmed, at which time subjects will be followed every 12 weeks by phone/email (if no recent medical charting available) to collect data on survival and any subsequent anti-cancer treatment that may have been administered. Follow-up will continue until death, withdrawal of consent, or the end of the study, whichever occurs first. At the conclusion of the study, all remaining subjects who have received at least 1 dose of study treatment will be offered enrollment in a long-term follow-up study and continue to be followed for survival.

Additional guidelines specific to the Phase 1 and 2 portions of the study are provided below.

Phase 1: Dose Evaluation, Assigned Arms

The epacadostat dose will be evaluated based on a 3+3 design utilizing protocol defined DLT criteria:

Cohort[3]	0/3 subjects have DLT[1]	1/3 subjects have DLT[1]	<2/6 subjects have DLT[1]	≥2 in a cohort have DLT[1,2]
Dose Cohort 1 [4] CRS-207 + 100 mg BID IDO	Escalate to Dose Cohort 2	Expand Dose Cohort 1 to 6 subjects	Escalate to Dose Cohort 2	De-escalate to Dose Cohort -1 (CRS-207 + 50 mg BID IDO)[3]
Dose Cohort 2 CRS-207 + 300 mg BID IDO	Expand cohort to 12 subjects with paired biopsies	Expand Dose Cohort 2 to 6 subjects	Expand cohort to 12 subjects with paired biopsies	Dose expand with 100 mg BID IDO

1. DLT period is 21 days after first dose of CRS-207.
2. In the case that a cohort is closed to enrollment, subjects who are ongoing at that dose level without DLTs may continue treatment at the assigned dose level at the discretion of the Investigator.
3. Evaluation of Dose Cohort -1 will enable the same 3+3 rules for dose cohort expansion or de-escalation to 25 mg (Dose Cohort -2). Evaluation of Dose Cohort -2 will enable the same 3+3 rules for dose cohort expansion. If Dose Cohort -2 is not tolerated, the Arm will be terminated.
4. As an added safety measure, Dose Cohort 1 will have a staggered enrollment of no more than 1 new subject treated per week during the dose escalation phase. Thereafter, a decision to further stagger combination enrollment will be made by the Safety Review Committee (SRC) and will be based on emergent safety data.

BID = twice daily; DLT = dose-limiting toxicity

A Safety Review Committee (SRC) will be convened for the study, consisting of the Investigators who enrolled subjects in the study, the Lead Investigator, Study Medical Monitor, and Sponsor representatives. Adverse events, DLTs and safety data for all subjects will be reviewed on an ongoing basis by the SRC. Dose escalation and reduction decisions, determination of the recommended dose for expansion, and R2PD will be made by the SRC.

Additionally, up to 12 subjects will be enrolled in in the CRS-207 alone arm to assess the safety and tolerability of CRS-207 in subjects with platinum-resistant ovarian, fallopian or peritoneal cancer.

Phase 2: Randomized, 2-stage

Phase 2 will begin by assessing safety of the addition of pembrolizumab to CRS-207 and CRS-207/epacadostat; pembrolizumab will be administered at the 200 mg fixed dose level (as approved in other cancer indications). Phase 2 will initiate after the RP2D of CRS-207/epacadostat is determined in Phase 1 and approximately 12 subjects with paired biopsies have been dosed at that level.

A Safety Run-in will be completed since there are no precedent data on the addition of pembrolizumab to the planned drug combinations. Treatment of the first 6 randomized subjects in each treatment arm will be staggered, with no more than 1 subject treated per week, per arm. Subjects will be monitored during the Safety Run-in Period [the first 21 days] using the protocol defined DLT criteria. In the event ≥2 subjects in up to 6 (per arm) experience DLTs, the SRC will convene to determine if subsequent subjects enrolled will require a different dose level (per dose reduction table), or if additional subjects should be enrolled at a specified dose level to further assess safety and tolerability. In the event ≥2 subjects in the next 6 subjects (per arm) treated experience DLTs, the SRC will reconvene to determine if the dose will be further modified for the remaining subjects to be enrolled. The SRC may convene at any time during the Safety Run-in Period to review and evaluate available safety data as warranted by emerging safety data.

Safety Run-in Dose Levels and Dose Reduction Table

Dose level	pembrolizumab	epacadostat	CRS-207
1	200 mg	300 mg BID	1×10^9 CFU
-1	200 mg	100 mg BID	1×10^9 CFU
-2	Further dose reductions will be discussed and confirmed by the SRC based on emergent safety data.		

Phase 2 will utilize a 2-stage design. Subjects will be randomized 1:1 into 2 treatment arms. In the first stage, once the final dose is confirmed in the Safety Run-in, a total of 13 subjects will be randomized into each arm (total 26 subjects). If the phase 2 dose is modified, at least 13 subjects will be enrolled and treated at the final dose level in each arm. If the pre-specified objective response-rate (ORR) and progression-free survival (PFS) criteria for advancement in the 2-stage

design are met (≥1 response or median PFS ≥ 4.8 months) for an arm, an additional 14 subjects will be enrolled in that arm, for a potential total of 27 subjects per arm (up to 54 subjects total if both arms advance to stage 2).

In the event that during the safety run in there are 2 DLTs in 6 patients in the CRS-207/pembrolizumab arm but the CRS-207/pembrolizumab/epacadostat has 0 or 1 DLTs in 6 patients using the same dose levels as in the 2 arm combination, the SRC will review the data and may allow enrollment of another 3 subjects in each run-in to better define the toxicities.

DOSING, DOSAGE FORMS, AND ROUTE OF ADMINISTRATION:

CRS-207, live, attenuated, double-deleted *Listeria monocytogenes* encoding human mesothelin (*Lm* Δ*actA*/Δ*inlB* hMeso), is formulated as 1×10^9 CFU suspended in [redacted], filled into a single-use 2-mL glass vial with a gray butyl stopper and aluminum crimp seal with a flip off cap. 1.0 mL CRS-207 is diluted in sterile saline prior to IV infusion.

Epacadostat, an indoleamine 2,3-dioxygenase (IDO) 1 inhibitor, is available as 25 mg and 100 mg tablets packaged in high-density polyethylene bottles. Epacadostat will be dispensed for 3-week cycles for the duration of the study. Tablets are taken at the assigned dose BID in the morning and evening, approximately 12 hours apart.

Pembrolizumab, Pembrolizumab can be in liquid or lyophilized powder format in single-use vials. Refer to the package insert for dose preparation instructions.

ADU-CL-11 Treatment Cycles by Arm

Phase	Arm	Dose [1] / Route	Treatment Cycle
1	CRS-207/ IDO	CRS-207: 1×10^9 CFU by IV infusion over ~ 1 hour IDO: 100 mg or 300 mg BID Oral	CRS-207: Day 1 of each cycle (Cycles 1-6); Q6W thereafter IDO: BID starting Cycle 1 Day 2
	CRS-207	CRS-207: 1×10^9 CFU by IV infusion over ~ 1 hour	CRS-207: Day 1 of each cycle (Cycles 1-6); Q6W thereafter
2	CRS-207/ Pembro/ IDO	Pembro: 200 mg by IV infusion over 30 min CRS-207: 1×10^9 CFU by IV infusion over ~ 1 hour IDO: 300 mg Oral BID [1]	Pembro: Day 1 of each cycle CRS-207: Day 2 of each cycle (Cycles 1-6); Q6W thereafter IDO: BID starting Cycle 1 Day 3
	CRS-207/ Pembro	Pembro: 200 mg by IV infusion over 30 min CRS-207: 1×10^9 CFU by IV infusion over ~ 1 hour	Pembro: Day 1 of each cycle CRS-207: Day 2 of each cycle (Cycles 1-6); Q6W thereafter

BID = twice daily; CFU = colony-forming units; IDO = epacadostat; IV = intravenous; pembro = pembrolizumab; Q6W = once every 6 weeks

[1] RP2D of epacadostat based on Phase 1 dose-evaluation parameters and determined by the SRC; the phase 2 dose may be further adjusted during Phase 2 Safety Run-in

DOSE-LIMITING TOXICITY:

During Phase 1, the DLT evaluation period is defined as Cycle 1 (21 days).

During the Phase 2 Safety Run-in, the DLT evaluation period is defined as Cycle 1 (the first 21 days).

Non-Hematologic Events

For non-hematological events, a DLT is defined as any treatment-emergent adverse event (TEAE) not attributable to disease or disease-related processes that occurs during the DLT observation period (Cycle 1) and is Grade 3 or higher according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.

In addition, any use of systemic steroids or a study drug dose interruption lasting more than 7 days for an adverse event with an unclear relationship to study drug will be considered a DLT even if the other DLT criteria are not fulfilled.

The following non-hematological adverse events are NOT considered DLTs:

- Grade 3 aspartate aminotransferase (AST), alanine aminotransferase (ALT), or alkaline phosphatase levels persisting for <7 days;
- Grade 3 fatigue lasting <3 days;
- Grade 3 nausea or vomiting that has resolved to ≤ Grade 2 within 48 hours with standard antiemetic therapies;
- Grade 3 diarrhea that has resolved to ≤ Grade 2 within 48 hours with standard antidiarrheal therapies;
- Grade 3 fever;
- Grade 3 or 4 laboratory finding that is asymptomatic and rapidly reversible (returned to baseline or ≤ Grade 1 within 7 days) unless identified as clinically significant by the Investigator;
- Any Grade 3 or lower change in cholesterol or triglycerides or asymptomatic change in lipid profile; and/or
- Singular or non-fasting elevations in blood glucose (i.e. blood glucose excursions will be considered a DLTs if fasting blood glucose is elevated (Grade 3 or higher) on 2 separate occasions).

Hematologic Events

For hematologic events, a DLT is defined as follows:

- Grade 4 neutropenia lasting >7 days;
- Grade ≥3 febrile neutropenia;
- Grade 4 anemia;
- Grade 4 thrombocytopenia or ≥ Grade 3 thrombocytopenia lasting >7 days or associated with bleeding; and/or
- Dose delay >7 days secondary to myelosuppression.

Toxicities will be monitored throughout the study, and if the toxicity levels in any Arm are unacceptable (>33% of subjects), then dosing will be suspended until further review and consideration by the SRC.

INCLUSION AND EXCLUSION CRITERIA:

Inclusion Criteria

Individuals must meet all of the following requirements to be eligible to enroll in this study:

1. Female, 18 years of age or older
2. Histologically-confirmed disease

For Phase 1: Individuals with epithelial ovarian cancer, fallopian tube carcinoma, or primary peritoneal carcinomas who are considered to have platinum-resistant disease (defined as progression within 6 months from completion of platinum-based chemotherapy). The date should be calculated from the last administered dose of platinum therapy.

For Phase 2: Individuals with epithelial ovarian cancer, fallopian tube carcinoma, or primary peritoneal carcinomas who are considered to have platinum-resistant disease (defined as progression within 6 months from completion of a minimum of 4 platinum therapy cycles). The date should be calculated from the last administered dose of platinum therapy.

3. Measurable disease, as defined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

Phase 1 only: Individuals who do not have measurable disease (according to RECIST v1.1) but have assessable disease according to the Gynecologic Cancer Intergroup (GCIG) CA-125 criteria and require treatment, may be included if they meet all other criteria.

4. Agree to provide core tissue biopsies at baseline and at Cycle 2 Day 15
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
6. Available archived tumor tissue for central analysis
7. Adequate organ and marrow function, as defined by:
   - White blood cells ≥3000/μL
   - Absolute neutrophil count (ANC) ≥1500/μL
   - Absolute lymphocyte count ≥ 800/μL
   - Platelet count ≥100,000/μL
   - Serum albumin ≥3 g/dL
   - AST and ALT ≤2.5 × upper limit of normal (ULN) (<5 × ULN for subjects with liver metastases)
   - Total bilirubin ≤ the institutional ULN or conjugated bilirubin ≦ 1.2 × ULN (need only be tested if total bilirubin exceeds ULN) or ≤ 3 × institutional ULN if due to Gilbert's disease
   - Serum creatinine ≤1.5 × ULN or calculated creatinine clearance (CrCl) (estimated glomerular filtration rate [eGFR] can also be used in place of creatinine or CrCl) >50 mL/min for serum creatinine >1.5 × ULN
   - Hemoglobin ≥9 g/dL
   - International normalized ratio (INR) or prothrombin time (PT) ≤1.5 × ULN. Activated partial thromboplastin time (aPTT) ≤1.5 × ULN (unless receiving

anticoagulant therapy in which case values should be within therapeutic range of intended use)

Any other Grade 3 or higher lab abnormalities should be discussed and approved by the Study Medical Monitor prior to enrollment (even if not considered clinically significant)

8. Women of childbearing potential must agree to take appropriate precautions to avoid pregnancy, including the use of a medically acceptable method of highly effective contraception throughout the study and for 120 days after their final study drug administration. A barrier method of contraception must be employed regardless of other methods. Permitted methods that are at least 99% effective in preventing pregnancy should be communicated to the subject and their understanding confirmed.
9. Functional gastrointestinal tract (defined as no enterocutaneous fistulas and no proximal stomas). Individuals with a venting gastrostomy tube must be able to tolerate clamping for 2 hours following oral drug administration.
10. Provides informed consent and is willing and able to comply with all study procedures.

Exclusion Criteria

Individuals who meet any of the following exclusion criteria will not be eligible to participate in the study:

1. Platinum-refractory disease (defined as progression during the first platinum-based chemotherapy)
2. Major surgical procedure within 4 weeks prior to dosing
3. Inaccessible tumors or for whom biopsy is contraindicated
4. Clinically significant ascites
5. **Phase 2 only**: Previous treatment with >3 chemotherapy regimens for locally advanced or metastatic disease
    - Repeat exposure to the same regimen separated in time by more than 3 months counts as 2 regimens
    - Regimens given as adjuvant therapy or as maintenance therapy after disease relapse are not included
    - Targeted agents will be included in the count
    - Bevacizumab will not count if administered as a single agent

    (There is no limit on the number of prior regimens for subjects entered into Phase 1)
6. Active bowel obstruction, or hospitalization for bowel obstruction within 2 months prior to screening
7. Requires parenteral nutrition or other agents aimed at improving performance status
8. Hospitalization within 2 weeks prior to screening
9. Received any anticancer medication or therapy in the 21 days prior to first dose of study drug or any unresolved toxicity > Grade 1 from previous anticancer therapy, except for

stable chronic toxicities that are not expected to resolve (i.e. peripheral neurotoxicity, alopecia, fatigue, etc.). Palliative radiotherapy is allowed if completed at least 2 weeks prior to first dose of study treatment.

10. Prior monoclonal antibody treatment within 4 weeks before first dose of study drug, or not recovered (≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier
11. History of listeriosis or previous treatment with a *Listeria*-based immunotherapy
12. Known allergy to both penicillin and sulfa antibiotics
13. Any immunodeficiency disease or immune-compromised state (e.g. use of immunosuppressive agents) or had systemic steroids, TNF pathway inhibitors, or PI3 kinase inhibitors administered within 14 days prior to initiating study drug (use of inhaled or topical steroids or systemic corticosteroids <10 mg is permitted)
14. Received prior immune checkpoint inhibitors (e.g. anti-CTLA-4, anti-PD-1, anti-PD-L1, and any other antibody or drug specifically targeting T cell costimulation) or an IDO inhibitor. Individuals who have received experimental vaccines or other immunotherapies must obtain approval from the Study Medical Monitor to confirm eligibility.
15. Pregnant or breastfeeding; or intends to conceive a child from the start of screening through 120 days after the last dose of study drug
16. Clinically significant heart disease (such as unstable angina, myocardial infarction within 6 months of study initiation, congestive heart failure, or New York Heart Association Class III or IV heart failure, or arrhythmia requiring therapy)
17. Valvular heart disease that requires antibiotic prophylaxis for prevention of endocarditis, consistent with American Heart Association guidelines
18. History of any autoimmune disease which required systemic therapy in the past 2 years including but not limited to:
    - Inflammatory bowel disease (including ulcerative colitis and Crohn's Disease)
    - Rheumatoid arthritis
    - Systemic progressive sclerosis (scleroderma)
    - Systemic lupus erythematosus
    - Autoimmune vasculitis (e.g. Wegener's granulomatosis)
    - Central nervous system or motor neuropathy considered of autoimmune origin (e.g. Guillain-Barre Syndrome, Myasthenia gravis, multiple sclerosis)

    Individuals with vitiligo, Sjogren's Syndrome, interstitial cystitis, Graves' or Hashimoto's Disease, celiac disease, diabetes mellitus type 1, psoriasis, or hypothyroidism stable on hormone replacement will be allowed with Study Medical Monitor's approval
19. Diagnosed with another malignancy within the past 3 years (excluding a history of carcinoma in situ of the cervix, superficial non-melanoma skin cancer, superficial bladder cancer, or endometrial cancer that has been adequately treated)

20. Individuals with treated (surgically excised or irradiated) and stable brain metastases are eligible as long as the treatment was at least 4 weeks prior to initiation of study drug and baseline brain computed tomography (CT) with contrast or magnetic resonance imaging (MRI) within 2 weeks of initiation of study drug is negative for new brain metastases. Individuals with stable brain metastases must not require therapy with corticosteroids.
21. History of interstitial lung disease
22. Evidence of interstitial lung disease or active, noninfectious pneumonitis including symptomatic and/or pneumonitis requiring treatment.
23. Active infection requiring systemic therapy
24. History of organ transplant that requires use of immunosuppressive therapy
25. Received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including G-CSF, GM-CSF or recombinant erythropoietin) within 4 weeks prior to first dose of study drug.
26. Intercurrent illness that is either life-threatening or of clinical significance such that it might limit compliance with study requirements
27. History of alcohol dependence or use of illicit drugs (e.g. opioids, cocaine, amphetamines, or hallucinogens) that could potentially interfere with adherence to study procedures or requirements
28. Received a diagnosis of human immunodeficiency virus or human T-lymphotropic virus, or has a known history of, or is positive for, Hepatitis B (HBsAg reactive) or Hepatitis C (HCV RNA [qualitative] is detected)
29. Received any prophylactic vaccine within 14 days of first dose of study drug or received a live vaccine within 30 days of first dose of study drug
30. Has 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 that were placed more than 3 months prior to first dose of study drug.
31. Known or suspected allergy or hypersensitivity to yeast or any other component of CRS-207 (e.g. glycerol); or known allergy or reaction to any component of epacadostat formulation; or any history of severe hypersensitivity reactions to pembrolizumab, its excipients or any monoclonal antibody therapy
32. Currently receiving therapy with a UDP-glucuronosyltransferase 1A9 (UGT1A9) inhibitor including diclofenac, imipramine, ketoconazole, mefenamic acid, and probenecid. Individual may enter screening if therapy is able to be discontinued (a 7 days washout period is required prior to first dose of epacadostat, or 5 half-lives have elapsed for the specific UGT1A9).
33. Presence of a gastrointestinal condition that may affect drug absorption

34. Receiving monoamine oxidase inhibitors (MAOIs) or a drug which has significant MAOI activity (meperidine, linezolid, methylene blue) within the 21 days before screening
35. Any history of Serotonin Syndrome after receiving serotonergic drugs
36. History or presence of an abnormal electrocardiogram (ECG) that, in the Investigator's opinion, is clinically meaningful. Screening QTcF interval >480 ms is excluded. In the event that a single QTcF is >480 ms, the subject may enroll if the average QTcF for the 3 ECGs is <480 ms. For subjects with an intraventricular conduction delay (QRS interval >120 ms), the JTc interval may be used in place of the QTcF with Sponsor approval. The JTc must be <340 ms if JTc is used in place of the QTcF. Individuals with an intraventricular delay due to a left bundle branch block are excluded.

    Note: QTcF prolongation due to pacemaker may enroll if the JTc is normal.
37. Uses more than 4 g/day of acetaminophen
38. Has an unhealed surgical wound
39. Insufficient peripheral venous access to permit completion of the study dosing and compliance with study phlebotomy regimen
40. Participated in any other study in which receipt of an investigational new drug occurred within 28 days of first dose of study drug
41. Unwilling or unable to follow the study schedule for any reason

Dose Eligibility

CRS-207

Subjects must have adequate organ function as defined by the laboratory values in the table below prior to each dosing cycle where CRS-207 is administered. The Study Medical Monitor will be notified of any dose delays due to safety concerns (eg if the subject is recovering from an AE or pembrolizumab infusion reaction) and to discuss a plan to resume treatment. If a dose is delayed beyond 7 days post pembrolizumab infusion, the dose of CRS-207 should be withheld until the next Cycle. If a dose is delayed more than 2 weeks, contact the Study Medical Monitor for further instruction on continued dosing.

The dosing eligibility requirements for CRS-207 are as follows:

Hematologic	**Renal**	**Hepatic**
WBC ≥3000/µL ANC ≥1000/µL Platelets ≥100,000/µL Hemoglobin ≥8 g/dL	Creatinine ≤1.5 × ULN	AST/ALT ≤5 × ULN Bilirubin ≤ 1.5× ULN OR ≤ 3 × ULN if due to Gilbert's disease
ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ULN = upper limit of normal; WBC = white blood cell		

Epacadostat & Pembrolizumab

If the subject meets eligibility criteria for the study and is assigned or randomized to receive epacadostat BID and/or pembrolizumab, dosing may initiate and should continue per protocol. The Study Medical Monitor will be notified of any dose interruptions due to safety concerns (Section 5.4.1).

Pembrolizumab dosing may be delayed up to 2 weeks, after which time it will be considered missed and the subject would continue onto the next scheduled dose. If a dose is delayed more than 2 weeks, contact the Sponsor Medical Monitor for further instruction on continued dosing.

Subject Discontinuation

A subject may be removed from treatment for any of the following reasons:

- Occurrence of an adverse event that presents an unacceptable consequence or risk to the subject
- Subject has received treatment, and there is no longer potential for clinical benefit (treatment should continue beyond initial progression of disease if there is potential for clinical benefit)
- Noncompliance (failure to receive clinical study medication or treatment as mandated by the protocol, or failure to comply with protocol requirements)
- A subject becoming pregnant while on study drug
- Consent is withdrawn by the subject or legal representative
- Study is discontinued by the Sponsor

Subjects may withdraw consent or discontinue from the study at any time for any reason. Every effort will be made to follow all subjects for PD and survival.

DURATION OF SUBJECT PARTICIPATION:

The Screening Period may last up to 28 days. Treatment will continue as long as there is potential for clinical benefit except that pembrolizumab may be administered up to a maximum of 24 months. [redacted]. Subjects will be observed for survival until death, withdrawal of consent, or the end of the study, whichever occurs first. At the conclusion of the study, all remaining subjects who have received at least 1 dose of study treatment will be offered enrollment in a long-term observational study and continue to be followed for survival.

EFFICACY ASSESSMENTS:

- Tumor evaluation by radiographic imaging
  - CT with contrast or MRI in case of contrast dye allergy
  - Tumor response assessed using RECIST v1.1, modified Response Evaluation Criteria in Solid Tumors (mRECIST), and GCIG CA-125 criteria
- Circulating CA-125 tumor biomarker levels
- Survival (vital status)
- Pharmacokinetics and pharmacodynamics
- Immunological and tumor biomarker analysis on tumor biopsies, peripheral blood mononuclear cells, plasma, and serum

- Number of tumor infiltrating lymphocytes and ratio of CD8 to regulatory T lymphocytes (FoxP3)
- PD-L1 and mesothelin expression along with additional markers may be evaluated to explore the relationship to clinical response.

SAFETY ASSESSMENTS:

Safety parameters include serious adverse events, TEAEs, ECOG performance status, vital sign measurements, standard clinical laboratory parameters (serum chemistry, hematology, endocrine function, coagulation parameters, pregnancy testing and urinalysis), physical exam findings, and ECG parameters. Shedding (urine, oral swab, and rectal swab) and clearance (blood) of CRS-207 will also be monitored. [redacted]. Adverse events will be graded according to the NCI CTCAE v4.

STATISTICAL ANALYSES:

During Phase 1, dose escalation will be based on traditional escalation guidelines (3+3) to determine the RP2D and evaluate safety data (including DLTs and adverse events) of each planned treatment.

Phase 2 will be an open-label, randomized study design conducted in 2 stages to achieve up to 27 treated subjects per Arm. After 13 subjects in an Arm are randomized at the confirmed dose following the Safety Run-in (stage 1), an additional 14 subjects will be enrolled in that Arm (stage 2) if 1 or more subjects respond or if the median PFS is at least 4.8 months. If the criteria for either ORR or PFS are not met, the preliminary anti-tumor activity in the Arm will be rejected and no further subjects will be randomized to the Arm. If the Arm goes on to stage 2, a total of 27 treated subjects will be studied in that Arm. The Arm will be considered successful if 4 or more subjects respond or the median PFS is at least 4.8 months. If the criteria for either ORR or PFS are not met, the Arm will be rejected. This design is applied to each Arm independently. There are no formal comparisons planned between Arms. This is an exploratory study of each Arm where the sample size and ORR and PFS criteria for each stage are based on clinical judgement. The ORR criteria and number of subjects for each stage are based on a Simon minimax 2-stage design (null hypothesis that ORR ≤5% versus the alternative that ORR ≥ 20% with alpha = 0.05 and power = 0.80). The PFS criteria are based on the lower limit of the 95% CI based on a meta-analysis in the 3rd relapse patient population where the median PFS is 5.6 months, (95% CI: 4.8 to 6.2 months) (Hanker, 2012).

Descriptive statistics will be provided for selected demographic, safety, pharmacokinetic, and immunogenicity data by dose and time as appropriate. Descriptive statistics on continuous data will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may be presented. Response will be assessed using RECIST v1.1, mRECIST, and GCIG CA-125. PFS will be assessed using mRECIST, RECIST v1.1, and GCIG CA-125. OS will also be analyzed using Kaplan-Meier methods.

Table 1 SCHEDULE OF EVENTS: Phase 2 ONLY (Phase 1 Schedule of Events in Appendix F)

Study Phase	Screening	Treatment Period [1]													Follow-up Period						
	Screening	Cycle 1					Cycle 2					Cycle 3 and 4			Cycles 5 and Beyond				EOT [2]	Safety Follow-up[3]	Survival Follow-up
															Odd Numbered Cycles (5, 7, etc.)		Even Numbered Cycles (6, 8, etc.)				
Study Day	-28 to -1	1	2	3	8	15	1	2	3	8	15	1	2	8	1	2	1	2	ASAP After Last Dose	30 Days After Last Dose	Every 12 Weeks
Visit Window (Days)	-	-	-	-	±1	±1	±3	-		±1	±1	±3		±1	±3	-	±3	-		+5	±7
Study Procedures																					
Informed Consent	X																				
Inclusion/Exclusion Criteria	X																				
Randomization [4]		X																			
Medical History	X																				
Vital Signs, Height, Weight [5]	X	X	X	X			X	X	X			X	X		X	X	X	X		X	
Physical Examination [6]	X	X					X					X			X		X		X	X	
ECOG Performance Status	X	X			X	X	X				X	X			X		X			X	
Electrocardiogram [7]	X	X	X			X [7]	X	X				X	X		X	X				X	
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Prior and Concomitant Medications and Therapies [8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Survival and Additional Cancer Treatment Status [9]																					X
Laboratory/Sample Collection																					
Virology Screen [10]	X																				
Urinalysis	X																			X	
CD4 Count	X																				
Pregnancy Test [11]	X	X					X					X			X		X			X	
Clinical Hematology, Serum Chemistry, Liver Function [12]	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X		X	
Coagulation Panel [13]	X		X	X				X	X											X	
CA-125 Assessment [14]	X	X					X					X			X		X		X		X [9]
HLA-Typing [16]	X																				

Study Phase	**Screening**	**Treatment Period [1]**																	**Follow-up Period**		
	Screening	**Cycle 1**					**Cycle 2**					**Cycle 3 and 4**			**Cycles 5 and Beyond**				**EOT [2]**	**Safety Follow-up[3]**	**Survival Follow-up**
															Odd Numbered Cycles (5, 7, etc.)		**Even Numbered Cycles (6, 8, etc.)**				
Study Day	**-28 to -1**	**1**	**2**	**3**	**8**	**15**	**1**	**2**	**3**	**8**	**15**	**1**	**2**	**8**	**1**	**2**	**1**	**2**	**ASAP After Last Dose**	**30 Days After Last Dose**	**Every 12 Weeks**
Visit Window (Days)	**-**	**-**	**-**	**-**	**±1**	**±1**	**±3**	**-**		**±1**	**±1**	**±3**		**±1**	**±3**	**-**	**±3**	**-**		**+5**	**±7**
Endocrine/Thyroid Testing [17]	X	X										X			X				X		
Plasma for epacadostat PK [19]/PD [30]		X					X														
Whole blood for epacadostat epigenetics [29]		X																			
Whole Blood for PBMC [18]		X			X		X			X		X		X	X				X		
Serum/Plasma for Immune Monitoring [15]		X	X		X		X	X		X		X		X					X		
Shedding and Clearance [20]			X	X	X			X	X	X											
Tumor Biopsy [21]	X										X										
Archived Tumor Specimen	X																				
Tumor Evaluation [22]	X	Every 9 weeks (± 7 days)																		X	X
Blood for CRS-207 Surveillance [28]																			X		X
Investigational Product Administration																					
Pembrolizumab [27]		X					X					X			X		X				
CRS-207 [23]			X					X					X			X [23]		X			
Epacadostat [24]				X	← BID →																
Epacadostat Compliance & Accountability [25]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Other Concomitant Medication																					
Antibiotics [26]																			X		

Footnotes

1. **Treatment** will continue for as long as there is potential for clinical benefit except that pembrolizumab will continue for a maximum of 24 months. At Cycle 5 and beyond, additional clinic visits between administrations of pembrolizumab and CRS-207 will be conducted based on Investigator's discretion and clinical indication.
2. **EOT Visit** will occur as soon as determined that the subject will permanently discontinue study treatment, and at least 7 days after the last dose of CRS-207. If the EOT visit coincides with a regular study visit, the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT page in the eCRF. If the EOT Visit occurs >21 days after the last administration of study drug, procedures from the EOT and Safety Follow-up visits may be collected as a single Safety Follow-up Visit.
3. **Safety Follow-up Visit** will be scheduled 30 days (+5 days) post last dose of study treatment. If the subject begins another anticancer therapy before the Safety Follow-up Visit, every effort will be made to complete all of the Safety Follow-up Visit assessments prior to commencing the new therapy. If there is an adverse event in need of monitoring beyond the Safety Follow-up Visit, the subject will be followed until resolution or confirmed stability of the adverse event. If a CT scan was collected within 9 weeks (±7 days) of the Safety Follow-up Visit, then a CT scan at the Safety Follow-up Visit will not be mandatory.
4. **Randomization:** An IRT system will be used for randomization. Randomization may be done up to 3 days prior to Day 1. During the Safety run-in, enrollment will be staggered with no more than 1 new subject treated per week, per treatment arm. Thereafter, a decision to further stagger combination enrollment will be made by the SRC and will be based on emergent safety data.
5. **Vital signs**: measurements consist of seated BP, pulse, respiratory rate, and temperature. Pulse oximetry will be measured if clinically indicated. Weight will be taken on Day 1 of each cycle. Height is required at screening only. During CRS-207 infusion, vital signs will be obtained pre-infusion (- 5 minutes), then every 30 minutes (+/- 5 minutes) during infusion and every hour (+/- 5 minutes) during post-infusion follow-up. During pembrolizumab infusion, obtain vital signs prior to (-5 minutes) and immediately following (+ 5 minutes) each infusion.
6. P**hysical examinations:** A complete physical exam will be conducted at screening and Safety Follow-up Visits; symptom-directed physical examinations will be conducted on Day 1 of all other cycles and at the EOT visit. Physical exams may be conducted up to 3 days before dosing with CRS-207.
7. **Electrocardiogram:** Perform routine 12-lead ECGs with the subject in recumbent or semi-recumbent position after 5 minutes rest prior to each CRS-207 and pembrolizumab infusion, immediately after the infusion, and at 1-hour post infusion. If abnormal at 1-hour post-infusion, repeat until baseline achieved. After Cycle 7 frequency may be reduced to every 12 weeks unless clinically indicated. In order not to confound interpretation of the ECG, if anti-emetics or other prophylactic agents are given then these should be given after the pre-dose ECG rather than before. Obtain ECG [heart rate, PR interval, QT interval, QRS duration, QTcF (Fridericia's correction) in triplicate (collected within approximately a 5-minute window). For subjects randomized to receive epacadostat serial ECGs will be collected pre-dose and approximately 60 to 90 minutes after the first dose of epacadostat. Additional ECGs may be performed if clinically indicated and at the Safety Follow-up Visit.
8. **Concomitant medications** and cancer-related therapies and procedures will be recorded within 28 days before study treatment begins and 30 days after the last dose of study drug, or until the subject completes the Safety Follow-up Visit. In addition, all prior and post-study treatment anticancer therapy will be recorded in the eCRFs.
9. **Survival Status:** Once a subject has radiographic confirmed PD, discontinues study treatment or starts a new anticancer therapy, the subject moves into the Survival Follow-up phase. Subject will be contacted every 12 weeks (by phone/email is permissible if no recent (with 14 days) medical charting is available) to collect data on survival and any additional cancer-related therapies that may have been administered. Follow-up will continue until death, withdrawal of consent, or the end of the study, whichever occurs first.
10. **Virology** screen will include HIV antibody, hepatitis B (HBsAg), and hepatitis C (HCV-RNA, Qualitative). Virology screen will be performed by the site's local laboratory.
11. **Pregnancy test** is required for women of child bearing potential. Pregnancy testing will be performed by the site's local laboratory.
12. **Safety Labs**: Refer to Appendix A for complete list of clinical hematology, chemistry analytes. Day 1 blood draws may be taken up to 3 days before dosing with pembrolizumab and then again after the pembrolizumab infusion and before the infusion with CRS-207; additional time points may be obtained if clinically indicated. **To avoid inadvertent contamination of a central line (e.g. infusion ports, PICC lines), blood draws MUST NOT be collected from a central line for at least 4 days after infusion of CRS-207 has started.** If LFTs are found to be abnormal (>Grade 2), frequency of monitoring should be increased to once per week until LFTs have resolved to baseline at which time chemistry test monitoring will be performed according to institutional standards or approximately weekly, whichever is shorter. Liver function does not need to be monitored once per week indefinitely for persistent low-grade abnormalities. Appropriate liver function monitoring intervals should be discussed with the Study Medical Monitor. Hematology, chemistry and liver panel will be performed by the site's local laboratory.
13. **Coagulation panel** will include the following: D-dimer, fibrinogen, INR of PT, and aPTT; and will be collected pre-CRS-207 dose and one day post CRS-207 dose. INR should be monitored weekly for the first 4 weeks after initiation of coumarin-based anticoagulants (see Section 5.6.2 for anticoagulant restrictions) and upon discontinuation of epacadostat. Coagulation testing will be performed by the site's local laboratory. Additional tests should be performed as clinically indicated

14. **CA-125** will be assessed at screening as close to but no more than 14 days before the first study treatment, then on Day 1 of each cycle while on treatment (or every 3 weeks if subject dosing is delayed). Subjects who discontinue treatment for reasons other than PD should continue to have CA-125 assessed every 9 weeks until the start of a new anticancer therapy, documented PD, death, or the end of the study, whichever occurs first. Additional CA-125 time points collected per institutional standard should also be entered into the eCRF. Subjects considered CA-125 evaluable should have CA-125 repeated no earlier than 28 days if a CA-125 is reduced by 50% from baseline. See Appendix C for more details.
15. **Immune Monitoring:** Whole blood for immune monitoring will be drawn and processed into serum and plasma. Refer to the Laboratory Manual for collection and processing instructions. Samples will be sent to the central laboratory.
16. **HLA-typing:** should include type A and B of class I antigens, low resolution. HLA will be performed by the site's local laboratory.
17. **Thyroid panel:** collected at Screening, Cycle 1 Day 1, then on Day 1 of odd numbered Cycles only (Cycle 3, Cycle 5, Cycle 7, etc.) and will include: triiodothyronine (T3) or free triiodothyronine (FT3), free thyroxine (FT4), and thyroid stimulating hormone (TSH); additional thyroid function testing may be performed if clinically indicated. Blood draws may be taken up to 3 days before pembrolizumab infusion. **Additional endocrine testing for subjects receiving epacadostat**: collected at Screening, Cycle 1 Day 1, Cycle 3 Day 1 and then every 12 weeks thereafter (on Day 1 of Cycle 7, Cycle 11, Cycle 15, etc.) will include: adrenocorticotropic hormone, serum cortisol (taken between 8-9 AM), luteinizing hormone and prolactin.
18. **Whole Blood for PBMC:** Approximately 70 mL of whole blood to be processed as described in the Laboratory Manual. PBMCs will be drawn at the following timepoints: Day 1 and Day 8 of Cycle 1, Cycle 2, Cycle 4, then Day 1 of Cycle 5, Cycle 7 and at the EOT visit.
19. **Epacadostat PK sample:** (3.5 mL) plasma for epacadostat will be taken pre epacadostat-dose on Cycle 2 Day 1. Epacadostat will be administered in clinic on Cycle 2 Day 1 in order to collect pre-dose blood sample for PK.
20. **Shedding/clearance:** For subjects in the Safety Run-in at US sites only: urine, rectal swab, oral swab, and whole blood will be collected pre-CRS-207 dose, and at 6 hours, 18 to 24 hours, and Day 7 post-CRS-207 infusion end time on Cycle 1 and Cycle 2. **DO NOT use the central line for blood sample collection**. Additional assessments will be performed if results are positive for CRS-207 at the Day 7 time point. Samples will be sent to IHMA Central Laboratory.
21. **Tumor biopsies:** will be collected during the screening period (pre-first dose) and on Cycle 2 Day 15 (+7 days). Fine needle aspiration will not be acceptable. Samples will be sent to the Central Laboratory. Tumor biopsy should NOT be performed on the same day as CRS-207 or pembrolizumab administration. If additional biopsies are performed by Investigator for standard of care during the course of study, a sample should be retained for Sponsor research evaluation.
22. **Tumor evaluations:** will be performed using CT with contrast of the abdomen and pelvis (or MRI in case of contrast dye allergy) within 28 days prior to treatment, and repeated every 9 weeks (±7 days) after initiation of study drug using the same assessment technique. Subjects who discontinue treatment for reasons other than PD should continue to have their disease assessed by CT every 9 weeks (±7 days) until the start of a new anticancer therapy, documented PD, death, withdrawal of consent, or the end of study, whichever occurs first. Data from any standard of care CT scans may also be collected for tumor evaluation.
23. **CRS-207:** will be administered on Day 2 of each cycle via IV infusion over approximately 1 hour (no in-line IV filter should be used). After Cycle 6, CRS-207 will be administered every six weeks, at even numbered visits (Cycle 8, Cycle 10, etc.) Study Medical Monitor must be notified for dose delays as noted in Section 4.3.1. Before each CRS-207 infusion, subjects will be pre-medicated with acetaminophen and saline will be given immediately before and after infusion with CRS-207 (Section 5.5.2.1). Subjects will be observed for at least 4 hours after each infusion. Subjects who are not stable enough to be released at 4 hours after infusion should continue to be monitored until stable. Presence of fever alone does not indicate subject is not clinically stable. Document the time subject becomes stable in the medical records. **To avoid inadvertent contamination of a central line (e.g. infusion ports, PICC lines), DO NOT administer CRS-207 or saline through a central line during infusion or for 4 days following infusion. DO NOT flush the central line for any reason during and for 4 days after CRS-207 infusion.**
24. **Epacadostat**: Epacadostat will be administered orally starting on Day 3 and BID thereafter. Tablets will be taken at the assigned dose in the morning and evening, approximately 12 hours apart. Epacadostat will be administered in clinic on Cycle 2 Day 1 and Day 2 in order to collect pre-dose blood sample for PK. Epacadostat dosing does not apply to CRS-207/pembro arm.
25. **Epacadostat Diary**: At each visit, provide a dosing diary and instructions on recording each dose of epacadostat. Collect unused epacadostat and review competed dosing diary with subject at following visit.
26. **Antibiotics:** A 7-day course of antibiotics will be administered at the EOT visit AFTER blood has been collected for CRS-207 culture to ensure clearance of CRS-207. Antibiotic regimen must be completed prior to initiation of any other cancer-related therapy. 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 (refer to Section 5.6.3). Site personal will contact the subject by to confirm compliance with the antibiotic treatment and document in source and CRFs.
27. **Pembrolizumab:** will be administered on Day 1 of each cycle via IV infusion over 30 minutes (-5/+10 minutes).

28. **CRS-207 surveillance:** At EOT, blood for culture will be collected prior to initiation of antibiotics (if applicable, blood must also be collected through the central line port) to assess CRS-207 clearance. After EOT, blood for culture will be collected for CRS-207 surveillance at [redacted].
29. **Epacadostat epigenetics:** A baseline whole blood sample for epigenetics (to characterize cell populations at baseline) will be collected prior to subject's first dose of epacadostat for subjects randomized to receive epacadostat.
30. **Epacadostat pharmacodynamics:** the PD sample for kynurenine/tryptophan determination should be collected pre-epacadostat dose, fasted overnight (at least 8 hours) on Cycle 1 Day 1 and Cycle 2 Day 1 only for subjects randomized to receive epacadostat.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ActA	Actin assembly-inducing protein A
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
APC	Antigen presenting cells
aPTT	Activated partial thromboplastin time
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
BID	Twice daily
BP	Blood pressure
CA-125	Cancer antigen 125
CFU	Colony-forming units
CI	Confidence interval
C_{max}	Plasma concentrations attained the peak values
CR	Complete response
CrCl	Creatinine clearance
CRA	Clinical Research Associate
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DC	Dendritic cell
DILI	Drug-induced liver injury
DKA	Diabetic ketoacidosis
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOT	End-of-Treatment
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCIG	Gynecologic Cancer Intergroup
GCP	Good Clinical Practice
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GVAX pancreas	Irradiated, whole-cell, allogeneic tumor immunotherapy
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
hMeso	Human mesothelin
IB	Investigator's Brochure

Abbreviation	Definition
IBC	Institutional Biosafety Committee
IC_{50}	Half maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDO	Indoleamine 2,3-dioxygenase
IHC	Immunohistochemistry
IL	Interleukin
InlB	Internalin B
INR	International normalized ratio
irAE	Immune-related adverse events
IRB	Institutional Review Board
irRC	Immune-related Response Criteria
IRT	Interactive Response Technology
IV	Intravenous
Kyn	Kynurenine
LFT	Liver function test
LLO	Listeriolysin O
Lm	*Listeria monocytogenes*
MAOI	Monoamine oxidase inhibitors
MedDRA	Medical Dictionary for Regulatory Activities
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NK	Natural killer
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
PD	Disease progression
PFS	Progression-free survival
PK	Pharmacokinetics
PPS	Per-Protocol Set
PR	Partial response
PT	Prothrombin time
Q3W	Every 3 weeks
QD	Once daily
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event

Abbreviation	Definition
SAF	Safety Set
SAP	Statistical analysis plan
SCCHN	Squamous cell carcinoma of the head and neck
SD	Stable disease
SNRI	Serotonin/norepinephrine reuptake inhibitors
SRC	Safety Review Committee
SS	Serotonin Syndrome
SSRI	Selective serotonin reuptake inhibitors
T1DM	Type 1 diabetes mellitus
TCR	T cell receptor
TEAE	Treatment-emergent adverse event
T_{reg}	Regulatory T lymphocyte
Trp	Tryptophan
UGT1A9	UDP-glucuronosyltransferase 1A9
ULN	Upper limit of normal
US	United States

1 INTRODUCTION AND BACKGROUND INFORMATION

1.1 Background

In the United States (US), ovarian cancer is the fifth leading cause of cancer-related death in women.[1,2] Approximately 21,290 patients were diagnosed with ovarian cancer in the US in 2015.[3] Epithelial ovarian cancer is the most common and lethal form of ovarian cancer.[4] Prognosis for survival depends on the stage of the disease at diagnosis. However, most women are diagnosed with advanced stage ovarian cancer, with a 5-year survival of only 30%.[1,2,5]

For patients with advanced stage ovarian cancer, surgical removal of the tumor is generally performed. Standard of care for these patients is then platinum-based combination chemotherapy. However, of the 60% to 80% of patients who present with advanced disease and who respond to first-line chemotherapy, more than 75% will develop resistant or recurrent disease.[6] Ultimately, almost all patients develop platinum resistance.[6]

Platinum-free interval, or the interval of time before disease recurrence, is a strong predictor of treatment outcome.[7] Outcome following platinum-based chemotherapy is categorized as follows:

- Platinum-sensitive – Patients whose disease responds but recurs >6 months from completion of platinum-based chemotherapy;
- Platinum-resistant – Patients whose disease responds but recurs <6 months from completion of platinum-based chemotherapy; or
- Platinum-refractory – Patients whose disease fails to respond.

Patients with platinum-sensitive disease can be re-treated with a platinum-based chemotherapy. However, treatment options for platinum-resistant patients are limited. The most active single agent therapies for patients with platinum-resistant disease include pegylated liposomal doxorubicin, paclitaxel, and topotecan.[8] Tumor response rates are in the range of 10% to 15% and overall survival (OS) is approximately 12 months.[9] When given in combination, these agents result in increased toxicity with no demonstrable improvement in outcome.[6,10-12]

The AURELIA trial[6] studied the addition of bevacizumab to single agent chemotherapy in patients with platinum-resistant disease. An improvement in progression-free survival (PFS) but not OS was noted. Objective response rate (ORR), determined using Response Evaluation Criteria in Solid Tumors (RECIST), in patients receiving bevacizumab-containing therapy was 27.3%, compared with 11.8% in subjects receiving chemotherapy alone. Importantly, the hazard ratio for PFS was 0.48 (95% confidence interval [CI]: 0.38 to 0.60), and the OS hazard ratio was 0.85 (95% CI: 0.66 to 1.08) when compared with chemotherapy alone. In November 2014, the US Food and Drug Administration (FDA) approved treatment of platinum-resistant recurrent ovarian cancer with bevacizumab and pegylated liposomal doxorubicin, paclitaxel, or topotecan.

Five-year survival rates for patients treated with platinum-based regimens are approximately 20% to 25%.[13] While this is a substantial improvement over the 5% to 10% survival rate reported for patients with advanced disease in the pre-platinum era, ovarian cancer still remains a formidable challenge and new treatment approaches are needed. For patients with platinum-resistant disease, the unmet medical need remains significant.

1.1.1 Immune Resistance in Cancers

The importance of immune surveillance in controlling the outgrowth of neoplastically transformed cells has been known for decades.[14] The inability of the immune system to control tumor growth does not appear to result from an inability to recognize the tumor as foreign. Tumor cells have been shown to evade immune destruction despite displaying recognizable antigens on their surface and despite the presence of high-avidity T cells that are specific for these antigens.[15,16] Histologic evaluation of many human cancers shows extensive infiltration by inflammatory and immune cells,[17] suggesting that the immune system responds to malignancy, albeit less effectively than needed to eradicate the tumors. These observations have led to the hypothesis that failure of the immune system to generate an effective response to malignancy could be the result of inadequate stimulation or exaggerated negative regulation. A combination of immunotherapy agents that stimulate an immune response targeted to tumor cells combined with the relief of negative regulation should synergize in allowing the immune system to generate a response leading to enhanced tumor rejection.

In recent years, several immune-targeted agents have been approved by the FDA for cancer treatment. While single agent activity has consistently been reported, combining immunotherapies that target distinct immune pathways has the potential to further enhance the depth and breadth of the anti-tumor immune response over single agents. Multiple immune mechanisms have been shown to be present concurrently in the tumor microenvironment, suggesting that combination therapies may be required for optimal therapeutic effect.[18,19] Several areas of opportunity exist where therapeutic intervention could be effective when combined. These areas include (1) promoting the antigen recognition and presentation functions of antigen presenting cells (APCs), (2) promoting the production of protective T cell responses, and (3) overcoming immune suppression in the tumor bed.[20]

1.1.2 CRS-207

1.1.2.1 Mesothelin as an Immunotherapy Target

Mesothelin is a tumor-associated antigen with limited expression on the surface of mesothelial cells lining the pleura, peritoneum, and pericardium, but highly expressed in several human tumors, including ovarian cancer, pancreatic cancer, non-small cell lung cancer (NSCLC), and mesotheliomas, but not in normal cells from the pancreas and ovary.[21] While mesothelin expression was detected in 20/21 of ovarian cancers in an earlier limited immunohistochemistry (IHC) study,[22] another study with 70 ovarian tumor samples using a combination of expression profiling, reverse transcription polymerase chain reaction confirmation, and IHC methods demonstrated that strong mesothelin expression was observed in approximately 65% of all samples evaluated, ranging from Grade 1 to 3 epithelial ovarian cancer, clear cell, endometrioid, and serous tumor types.[23] In contrast, in the same study, mesothelin expression was observed in 20/21 serous tumors evaluated, demonstrating the strong correlation between expression of this tumor-associated antigen and ovarian malignancy. This identifies mesothelin as an attractive target for active tumor-specific immunotherapy.

1.1.2.2 *Listeria monocytogenes*-Based Immunotherapy

Listeria monocytogenes (*Lm*) is an attractive platform for the presentation of tumor-associated antigens and activation of an immune response directed against cancer cells. *Lm* provides both a potent stimulation of innate immunity and also stimulates an adaptive immune response through recruitment and activation of $CD4^+$ and $CD8^+$ T cell immunity specific for the encoded heterologous antigens.[24-27] However, since wild-type *Lm* is a food-borne pathogen, the live-attenuated double-deleted *Lm* platform strain (*Lm* Δ*actA*/Δ*inlB*), known as ANZ-100, has deletions of 2 genes, *actA* and *inlB*. These genes encode the virulence-determinant proteins actin assembly-inducing protein A (ActA) and Internalin B (InlB), the 2 proteins which facilitate cell-to-cell spread and invasion of non-phagocytic cells, in particular hepatocytes. Deletion of *actA* and *inlB* in ANZ-100 results in the retention of the immunostimulatory potency of the fully virulent pathogen but with 1,000-fold attenuation of virulence in mice as compared with wild-type *Lm*.[28]

Uptake of ANZ-100 by macrophages and other phagocytic cells in the liver and spleen is still retained and results in a local inflammatory response as well as activation and recruitment of natural killer (NK) cells and T cells to the liver. ANZ-100 underwent clinical evaluation in a Phase 1 dose-escalation study of intravenous (IV) administration in adults with carcinoma and liver metastases and was found to be well tolerated at doses up to 3×10^8 colony-forming units (CFU).[29]

ANZ-100 was subsequently engineered to express mesothelin, resulting in CRS-207 (*Lm* Δ*actA*/Δ*inlB*/human mesothelin [hMeso]). CRS-207 contains an hMeso expression cassette integrated at the *inlB* locus. After uptake of CRS-207 by DCs and macrophages, mesothelin is expressed and released into the cytosolic compartment and subsequently processed through the endogenous major histocompatibility complex Class I presentation pathway, resulting in activation of mesothelin-specific cell-mediated immunity. Other mechanisms to activate mesothelin-specific, cell-mediated immunity may include uptake and cross-presentation of antigens by DCs and other cells after infection by CRS-207 and apoptosis.

1.1.2.3 Summary of Nonclinical Studies for CRS-207

Refer to the current CRS-207 Investigator's Brochure (IB) for additional details regarding nonclinical study data.

1.1.2.4 Summary of Clinical Studies for CRS-207

CRS-207 is being evaluated in multiple clinical studies and multiple oncologic indications. CRS-207, either alone or in combination (sequential or concomitant) with other investigational or approved agents, has been administered to more than 350 subjects with advanced cancers. CRS-207 administered with pembrolizumab is being evaluated in multiple oncologic indications; no safety or efficacy data is currently available. Initial data from an ongoing clinical study of CRS-207 with agents targeting the PD-1 blockade (i.e. nivolumab) in patients with pancreatic cancer suggests an acceptable tolerability profile.

A complete summary of current clinical information on CRS-207 is provided in the IB.

A Phase 1, first-in-human, multiple-dose, dose-escalation trial (VAC07001) was completed in adults with treatment-refractory malignant mesothelioma, advanced NSCLC, or advanced carcinoma of the ovary or pancreas. The maximum tolerated dose (MTD) was 1×10^9 CFU; CRS-207 was generally well tolerated. While the study enrolled subjects with multiple disease types

and was not powered to assess survival, 6/17 subjects (with prior immunotherapy or subsequent radiation) survived at least 15 months after receiving the first dose of CRS-207.

1.1.3 Epacadostat

Indoleamine 2,3-dioxygenase (IDO) 1 is an enzyme that contributes to tumor-derived immune suppression. Overexpression and upregulation of IDO1 depletes tryptophan (Trp) and increases Trp catabolites, including kynurenine (Kyn), which have been implicated in dendritic cell (DC) maturation and T cell growth arrest and cell death.[30] Inhibition of IDO1 may enhance the function of APCs, increase the number of $CD8^+$ T cells, and, at the same time, decrease the number of regulatory T lymphocytes (T_{regs}) infiltrating the tumor. Blocking IDO1 may also allow host T_{regs} to be "reprogrammed," resulting in enhanced $CD8^+$ T cell responses.[31] Therefore, adjuvant strategies designed to circumvent the endogenous immunosuppressive pathways, such as the IDO1 pathway, could offer ways to enhance immunotherapy efficacy.

Epacadostat (also referred to as INCB024360) is a novel, potent, and selective inhibitor of the enzyme IDO1. In cell-based assays, epacadostat potently inhibits IDO1 in both human tumor cells and human DCs resulting in reduced Trp to Kyn conversion (half maximal inhibitory concentration [IC_{50}] values: 7.1 to 12.7 nM). Epacadostat does not significantly inhibit other proteins that could impact Trp catabolism.

1.1.3.1 IDO Inhibition as a Target for Cancer

Recent interest has focused on the role of IDO1 as a mechanism of induction of tolerance to malignancy.[32] IDO1 is a heme-containing, monomeric oxidoreductase that catalyzes the degradation of the essential amino acid Trp to N-formyl-kynurenine. Kyn can be subsequently metabolized through a series of enzymatic steps to nicotinamide adenine dinucleotide. IDO1 is the first rate-limiting enzyme in one of the breakdown pathways of Trp. In another pathway, Trp hydroxylase catalysis of Trp leads to the formation of serotonin and melatonin.

The expression and activity profiles of IDO1 are distinct from those of Trp dioxygenase, an enzyme predominantly expressed in the liver that catalyzes the same enzymatic reaction as IDO1 and maintains proper Trp balance in response to dietary uptake. In contrast to Trp dioxygenase, IDO1 is expressed in a variety of tissues, with particularly high levels found in areas of contact with potential sources of immune challenge (e.g. gut, respiratory tract, placenta, and spleen), consistent with a role for regulating Trp metabolism in a local microenvironment.[33] Within the immune system, IDO1 activity is specifically induced in cells such as DCs and macrophages at localized sites of inflammation.[34]

IDO1-driven oxidation of Trp results in a strong inhibitory effect on the development of T cell-mediated responses by blocking T cell activation and inducing T cell apoptosis.[35] Both the reduction in local Trp levels and the production of Trp catabolites that are inhibitory to cell proliferation contribute to the immunosuppressive effects.[36] IDO1 activity also promotes the differentiation of naïve T cells to cells with a regulatory phenotype (T_{reg}).[37] Since increased T_{reg} activity has been shown to promote tumor growth and T_{reg} depletion has been shown to allow an otherwise ineffectual anti-tumor immune response to occur,[38] IDO1 expansion of T_{reg} may provide an additional mechanism whereby IDO1 could promote an immunosuppressive environment.

The biological relevance of IDO1 inhibition to immune tolerance was first demonstrated when it was shown that treating mice with a small molecule inhibitor of the IDO1 pathway, 1-methyl- Trp,

maintains immune tolerance to allo-antigens present in the fetus, and allows pregnancy to persist, whereas IDO inhibition results in immune-mediated fetal loss.[39] A critical role for IDO1 in immunomodulation has been confirmed in numerous animal models, including models of allograft tolerance, inflammation, and cancer.[33] While IDO1 inhibition can exacerbate disease in models of autoimmune disorders,[33] IDO1 null mice show no evidence of susceptibility to developing spontaneous autoimmunity or alterations in immune system development,[35] suggesting that IDO1 inhibition, in a therapeutic setting, may produce minimal side effects in subjects without pre-existing autoimmune conditions.

Within the context of cancer, there are several lines of evidence to suggest that IDO1 is a key regulator of the immunosuppressive mechanisms responsible for tumor escape from immune surveillance. Several groups have demonstrated that blockade of IDO1 activity can directly influence the ability of tumor-bearing animals to reject tumors.[40,41] In addition, studies with 1-methyl-tryptophan, demonstrate that IDO1 inhibition dramatically increases the efficacy of various chemotherapeutic agents (e.g. platinum compounds, taxane derivatives, cyclophosphamide) without increased toxicity.[41] Although the specific mechanisms responsible for this potentiation remain to be fully elucidated, the effects were not observed in T cell deficient animals, suggesting that improved therapeutic efficacy may result from disablement of immunosuppressive mechanisms within the tumor microenvironment.

Based on studies examining serum levels of Trp and Kyn, IDO1 appears to be chronically activated in patients with cancer, and IDO1 activation correlates with more extensive disease.[42,43] IDO1 is overexpressed in a wide variety of human tumor cell types, as well as by the DCs that localize to the tumor-draining lymph nodes.[40,44] Increased expression of IDO1 in tumor cells has been shown to be an independent prognostic variable for reduced OS in subjects with melanoma, ovarian, colorectal, and pancreatic cancers.[45-50]

Together, these results suggest that the IDO1 pathway is a key regulatory element responsible for the induction and maintenance of tumor immune tolerance. Small molecule inhibitors of IDO1 may provide an innovative and tractable method to treat malignancies either alone or in combination with chemotherapeutics and/or immunotherapy-based strategies.

1.1.3.2 Summary of Nonclinical Studies for Epacadostat

Refer to the current epacadostat IB for details on nonclinical study data.

1.1.3.3 Summary of Clinical Studies for Epacadostat

At least 10 Phase 1 and 2 Incyte-sponsored clinical studies have either been completed or are ongoing. Five investigator-sponsored clinical studies have either been completed or are ongoing. At least 890 subjects have been enrolled and received at least 1 dose of epacadostat in Incyte-sponsored studies, and 47 subjects were enrolled and received at least 1 dose of epacadostat in investigator-sponsored studies.

In the initial Phase 1 multicenter, open-label, dose-escalation study in subjects with refractory solid tumors by Incyte Corporation (study INCB 24360-101), epacadostat (INCB024360) was generally well tolerated in subjects with refractory solid tumors at doses of up to 700 mg BID, and there appeared to be no correlation of dose with toxicity. Of the 52 subjects who were administered INCB024360, the median duration of treatment was 51.5 days. Eight subjects (15.4%) had an AE leading to death; of these 8 subjects, the cause of death was disease progression for 7 subjects and

hypoxia for the remaining subject. Twenty-five subjects (48.1%) had an SAE during the study. Serious adverse events were observed in all 8 treatment groups. The most frequently reported SAE was disease progression (4 subjects, 7.7%), followed by abdominal pain, nausea, and hypoxia (3 subjects each, 5.8%). Treatment-emergent AEs were reported in all subjects. Fatigue and nausea were the most frequently reported treatment-related AEs (25 subjects each, 48.1%). The incidence and severity of fatigue were not dose related. Thirty subjects (57.7%) had treatment-emergent AEs ≥ grade 3 in severity and 7 subjects (13.5%) had a treatment-emergent AE leading to discontinuation of study drug and withdrawal from the study. Two dose limiting toxicities (DLTs) occurred; 1 DLT of radiation pneumonitis at the 300 mg BID dose level and 1 DLT of fatigue at the 400 mg BID dose level. A maximum tolerated dose (MTD) was not determined. There were no clinically meaningful changes or trends noted in clinical hematology, chemistry, or urinalysis results or for vital signs, electrocardiograms, or physical examinations.

In Study INCB 24360-201 (epacadostat + ipilimumab), 50 subjects were enrolled by the data cutoff (29 OCT 2015) and were treated with epacadostat 300 mg BID (i.e. subjects treated with 300 mg BID and subjects treated with 300 mg BID who subsequently reduced to 100 mg BID), 100 mg BID, 25 mg BID, 50 mg BID, 75 mg TDD (50 mg AM and 25 mg PM), and 50 mg BID intermittent doses (2 weeks on and 1 week off), all in combination with the anti−CTLA-4 antibody ipilimumab (3 mg/kg IV every 3 weeks).

In the initial Phase 1 dose-escalation portion, 5 of the 7 subjects receiving epacadostat 300 mg BID in combination with ipilimumab developed clinically significant ALT elevations; therefore, the study was amended to evaluate lower epacadostat doses. A preliminary analysis of epacadostat exposure parameters and liver function tests (LFTs) was performed, and there was no evidence of a relationship between steady-state peak exposure or AUC and ALT level for subjects in this cohort.

Based on the preliminary unaudited data as of the data cutoff (29 Oct 2015), 5 subjects (10%) had treatment-emergent AEs leading to death. Four of the 5 subjects had a single treatment-emergent AE (sepsis syndrome, intracranial hemorrhage, osteomyelitis, and multi-system failure) leading to death. One of the 5 subjects had multiple treatment-emergent AEs (hypotension, confusion, atrial fibrillation, bradycardia, acute kidney injury, cardiogenic shock) leading to death. None of these deaths were considered by the investigator to be causally related to treatment with epacadostat. Twenty-seven subjects (54.0%) had an SAE. Serious AEs were observed in the 300 mg BID, 25 mg BID, 50 mg BID, 50 mg BID intermittent, and 75 mg TDD dose groups. The system organ classes with the most frequently reported SAEs were gastrointestinal disorders (10 subjects, 20.0%), infections and infestations (7 subjects, 14%), and general disorders and administration site condition and investigations (6 subjects each 12.0%). The most frequently reported SAEs were increased ALT and AST (5 subjects in the 300 mg BID and 1 subject in the 50 mg BID group) followed by colitis (4 subjects total with 2 subjects in the 25 mg BID group, 1 subject in the 50 mg BID, and 1 subject in the 50 mg BID intermittent group). In the 75 mg TDD group 2 SAEs occurred in 1 subject each (fall and rash).

Treatment-emergent AEs were reported in 49 subjects (98.0%). Fatigue was the most frequently reported treatment-emergent AE (33 subjects, 66.0%) followed by rash (27 subjects, 54.0%; includes the preferred terms rash, rash generalized, rash macular, rash maculopapular, and rash pruritic). More than half of subjects (64.0%) had treatment-emergent AEs ≥ grade 3 in severity.

Nineteen subjects (38.0%) had a treatment-emergent AE leading to discontinuation of epacadostat. Five of the 7 subjects (71.4%) treated in the 300 mg BID cohort, 4 of the 8 subjects (50.0%) treated in the 25 mg BID cohort, 7 of the 18 subjects (38.9%) treated in the 50 mg BID cohort, and 3 of 9 subjects (33.3%) treated in the 50 mg BID intermittent dose cohort discontinued epacadostat because of treatment-emergent AEs. No subjects in either the 100 mg BID group or the 75 mg TDD group had a treatment-emergent AE leading to discontinuation of epacadostat.

In a recent ongoing Incyte Corporation Phase 1 study (INCB 24360-202), safety, efficacy, and tolerability of the combination of pembrolizumab at a dose of 2 mg/kg IV every 3 weeks in combination with epacadostat at doses of 25 mg BID to 300 mg BID in subjects with various, advanced or metastatic solid tumors is being evaluated. A total of 60 subjects were enrolled as of 29 October 2015: 25 mg BID (n=4) and, 50 mg BID (n=20), 100 mg BID (n=18), and 300 mg BID (n=18). Preliminary results from this study showed that one grade 3 rash (8%) was reported in the 50 mg BID cohort and this was found to be DLT based on the extent of rash. The most common all grade immune-related AEs were rash (16%), diarrhea (16%), dyspnea (8%), pruritus (8%), and headache (8%). The ORR per modified RECIST v1.1 (mRECIST) was 71% (5/7), and disease control rate (DCR; CR+PR+stable disease) was 100% (7/7) (note: calculations included only evaluable subjects for response).

Based on the preliminary, unaudited data as of the data cutoff (29 Oct 2015), no Grade 4 treatment-related AEs were reported. Three subjects (5%) discontinued for a treatment-related AE: grade 3 arthralgia, grade 3 AST increased, and grade 2 nervous system disorder. No treatment-related deaths occurred. Treatment-emergent AEs were reported in 44 subjects (73.0%). The most frequently reported AEs were rash (27%) followed by fatigue (23%). Rash includes the preferred terms rash, rash generalized, rash maculopapular, rash pruritic, and rash follicular.

Preliminary data from Study INCB 24360-210 (600 mg BID of epacadostat versus 20 mg BID of tamoxifen in Stage III or IV epithelial ovarian cancer) are available as of the data cutoff on 29 October 2015. This phase 1 study is a completed monotherapy study in subjects with biochemically recurrent-only epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube carcinoma after complete remission with first-line chemotherapy. At the time of the cutoff, 42 Forty-two subjects were enrolled (22 in the epacadostat treated group and 20 in the tamoxifen-treated group); 21 subjects (50.0%) discontinued due to disease progression, 15 subjects (35.7%) discontinued due to study termination, and 6 subjects (14.3%)withdrew due to treatment-emergent AEs. Based on the preliminary unaudited data through that date, no subject had an AE leading to death. Two subjects (4.8%) had an SAE. One SAE was reported in the epacadostat group (abdominal pain), and 1 SAE was reported in the tamoxifen group (ascites). The system organ classes with the most reported treatment-emergent AEs in the epacadostat group were general disorders and administration site conditions and gastrointestinal disorders (13 subjects each, 59.1%). Fatigue was the most frequently reported treatment-emergent AE in the epacadostat group (8 subjects, 36.4%), followed by nausea (6 subjects, 27.3%) and abdominal distention, constipation, and vomiting (4 subjects each, 18.2%). This study was terminated by the sponsor. No safety concerns with epacadostat were identified.

Epacadostat 600 mg BID was well-tolerated. Twenty-two subjects received at least 1 dose of epacadostat with a median exposure of 56.0 days and a median average total daily dose of 1200 mg. Twenty subjects received at least 1 dose of tamoxifen with a median exposure of 61.0 days and a median average total daily dose of 40 mg. No subject had an AE leading to death. Two

subjects (4.8%) had SAEs: 1 subject in the epacadostat group (abdominal pain) and 1 subject in the tamoxifen group (ascites). Treatment-emergent AEs were reported in 32 subjects (76.2%) with 17 subjects (77.3%) in the epacadostat group and 15 subjects (75.0%) in the tamoxifen group. Fatigue was the most frequently reported treatment-emergent AE in the epacadostat group (8 subjects, 36.4%), followed by nausea (6 subjects, 27.3%), rash (5 subjects, 22.7%), and abdominal distention, constipation, and vomiting (4 subjects each, 18.2%).

The most frequently reported immune-related AEs in the epacadostat group were skin-related, with 5 subjects (22.7%) reporting rash (2 with rash maculopapular, 1 with rash papular, 1 with rash erythematous, and 1 with rash) and 2 subjects (9.1%) reporting pruritus. Two subjects had maculopapular rashes that were ≥ grade 3. All other skin-related treatment-emergent AEs were < grade 3.

Seven subjects in the epacadostat group (31.8%) had a treatment-emergent AE ≥ grade 3 in severity including maculopapular rash (2 subjects), and increased GGT, vomiting, abdominal pain, hypertension, and hyponatremia (1 subject each).

The majority of subjects had normal hematology and clinical chemistry laboratory assessments at baseline, and the values remained normal throughout the study. Overall, no clinically meaningful changes or trends in vital sign measurements or 12-lead electrocardiogram findings were observed.

- The IB provides the most current and complete information on ongoing clinical studies INCB24360-203, Phase 1/2 open-label study of epacadostat administered in combination with MEDI4736 (durvalumab) in subjects with advanced melanoma, NSCLC, pancreatic cancer, or SCCHN
- INCB 24360-204, a Phase 1/2 study of the safety, tolerability, and efficacy of INCB24360 administered in combination with nivolumab in select advanced cancers, including melanoma, NSCLC, CRC, SCCHN, ovarian cancer, and B cell NHL or HL (including DLBCL) in Phase 1 and Phase 2, and glioblastoma in Phase 2.

1.2 Rationale for CRS-207, Epacadostat, and Pembrolizumab Immunotherapy in Advanced Ovarian Cancers

The adaptive immune system plays a key role in anti-tumor immune response by targeting cancer-specific antigens expressed by tumor cells.[51] Histologically, cancer cells show infiltration by immune cells. However, immune-mediated elimination is not possible due to the immunosuppressive state of the ovarian cancer microenvironment, resulting from the secretion of interleukin (IL)-4, IL-1β, vascular endothelial growth factor, and prostaglandin-E2.[51] These recruit immunosuppressive T_{regs}, and inhibit $CD4^+$ T cells.[51] An increase in T_{reg} activity has been shown to decrease survival.[52] In the context of cancer immunotherapy, the preferential inhibition of T_{reg} and an increase in tumor-infiltrating lymphocytes may enhance treatment-induced tumor-specific immunity, thereby improving efficacy.[53] In ovarian cancer cells, the high level of IDO expression results in a reduction of tumor-infiltrating lymphocytes, which has been associated with poor prognosis.[54] As IDO is a key regulator of immunosuppression, inhibition of IDO using epacadostat is a highly attractive strategy for ovarian cancer therapy.

The intracellular lifecycle of the live-attenuated double-deleted *Lm* platform strain used to create CRS-207 enables effective stimulation of $CD4^+$ and $CD8^+$ T cell immunity, known to be important for reducing tumor burden.[55] Multiple pathogen-associated molecular pattern receptors are

triggered in response to interaction with *Lm* macromolecules upon infection. This results in the pan-activation of innate immune effectors and release of Th-1-polarizing cytokines, exerting a profound impact in supporting the development of a $CD4^+$ and $CD8^+$ T cell response.[56-59]

Thus, CRS-207 and epacadostat may have a synergistic advantage: epacadostat inhibition of IDO1 can inhibit the immunosuppressive nature of the tumor microenvironment, thus allowing CRS-207 to most effectively initiate an anti-cancer immune response. The addition of a checkpoint inhibitor may enhance the immunotherapeutic potential of these agents by relieving the adaptive resistance mechanism on tumor-specific T cells. [redacted] Initial data from an ongoing clinical study of CRS-207 with agents targeting the PD-1 blockade (i.e. nivolumab) suggests an acceptable tolerability profile.

With the addition of pembrolizumab, it is hypothesized the reactivation and expansion of tumor-specific T cells in context of blocking the PD-1/PD-L1 inhibitory pathway may ultimately provide further enhanced anti-tumor activity. The current study is designed to evaluate whether CRS-207 with epacadostat and pembrolizumab effectively primes and sustains tumor-specific T cell responses and results in clinical benefit for patients with previously treated disease.

1.3 Potential Risks and Benefits of the Treatment Regimen

This study is the first to investigate the safety and immunogenicity of CRS-207 when administered with epacadostat and pembrolizumab in adults with platinum-resistant ovarian, fallopian, or peritoneal cancer.

1.3.1 CRS-207

The proposed dose level for this study (1×10^9 CFU) is the MTD as determined in the Phase 1 solid tumor dose escalation study (Protocol VAC07001), which included 2 ovarian cancer patients. It is also the dose administered in ongoing studies in other oncologic indications, which are demonstrating further safety and tolerance of this dose.

Treatment emergent adverse events (TEAEs) temporally related to CRS-207 administration which are common and may vary in degree of severity include fevers, chills, nausea, vomiting, fatigue, headache and changes in blood pressure; generally, these were reported as immediate, transient, and mild and resolve within 48 hours following CRS-207 infusion. Changes in hepatic enzyme levels and hematological parameters (lymphopenia) are also anticipated to varying degrees of severity. These effects are likely a consequence of the mechanism of action of CRS-207 through the activation of the innate immune system and release of proinflammatory cytokines and chemokines. Some of these infusion-related events may be mitigated by pre-medication with acetaminophen and administration of saline prior to and following CRS-207 infusion. Based on available results from clinical studies, continued clinical development of CRS-207 is warranted.

1.3.2 Pembrolizumab

1.3.2.1 Checkpoint Inhibitors

Programmed Death receptor-1 (PD-1) is a checkpoint protein on T cells that normally inhibits T cells from attacking other cells in the body. Overexpression of the ligand PD-L1 on cancer cells further evades immune attack by T cells. Checkpoint inhibitors, including antibodies targeting PD-1, block the PD-1/PD-L1 interaction and boost the immune response against cancer cells. Monoclonal antibodies targeting PD-1, including pembrolizumab and nivolumab, have been approved for use in multiple tumor types and are currently being studied in several additional indications.

1.3.2.2 Summary of Clinical Indications for Pembrolizumab

Pembrolizumab (Keytruda [US]), a humanized monoclonal antibody against the programmed death receptor-1 (PD-1) protein, has been developed by Merck & Co for the treatment of patients with cancer. Pembrolizumab is approved for treatment of patients with melanoma in several countries; in the US and EU it is approved for the treatment of adults with advanced, unresectable or metastatic malignant melanoma. Pembrolizumab has also been approved in several countries for the treatment of patients with NSCLC; in the US it is indicated for the treatment of metastatic NSCLC whose tumors express programmed death receptor ligand-1 (PD-L1) as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy. Patients with NSCLC and EGFR or ALK genomic tumor aberrations should also have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab. Pembrolizumab is also approved in the US for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after platinum-containing chemotherapy.

Pembrolizumab is not currently approved for treatment of platinum-resistant ovarian, fallopian, or peritoneal cancer and is being used as an investigational agent in this study. However, the approved package insert should be consulted for additional product information on storage, preparation and administration, contraindications, warnings/precautions, adverse reactions, and drug interactions.

The planned dose of pembrolizumab is 200 mg Q3W. As described in the approved label, existing exposure-response data and population pharmacokinetic modeling suggest 200 mg once Q3W is an appropriate fixed dose for pembrolizumab.

1.3.3 Epacadostat

As of 29 OCT 2015, 253 unique subjects have been exposed to INCB024360 as monotherapy (91 subjects) and/or in combination with checkpoint inhibitors (anti−PD-1 targeted therapy: 79 subjects; anti−PD-L1 targeted therapy: 33 subjects; and anti−CTLA-4 targeted therapy: 50 subjects). The most common expected treatment-emergent adverse events include diarrhea, nausea, vomiting, fatigue, and rash; increased hepatic enzyme levels are also expected. Of these, diarrhea, nausea, and vomiting are considered common serious events expected for epacadostat monotherapy. Consult the epacadostat IB for full reference safety information.

Theoretically, inhibition of IDO1 could cause an increase in serotonin levels that could precipitate a cluster of adverse events termed Serotonin Syndrome (SS) when administered alone or in combination with other serotonergic agents. This rare syndrome has been associated with some monoamine oxidase inhibitors (MAOIs) and combinations of serotonergic drugs.[60] The clinical manifestations of SS range from barely perceptible to lethal; onset is rapid (within 12 hours of drug[s] administration).

Based on preliminary studies in the rat, concentrations of epacadostat in the cerebrospinal fluid were below the quantifiable limit of detection (2 nM) after IV dosing, and total brain homogenate concentrations were approximately 15% of corresponding plasma concentrations. Therefore, epacadostat exhibits apparent limited penetration across the blood-brain barrier and is likely not associated with significant effects on Trp metabolism in the brain that might affect brain serotonin levels. In the INCB 24360-201 study, 12 of the 48 subjects enrolled as of 29 October 2014 received concomitant treatment with a selective serotonin reuptake inhibitors (SSRI) and epacadostat and 0 of 12 subjects exhibited SS. Although this represents a hypothetical risk only and has not been observed in clinical studies of epacadostat, use of MAOIs will be prohibited during the study. Subjects will be provided with an informative subject leaflet describing the signs and symptoms of the syndrome along with instructions to seek immediate medical care if any of these signs or symptoms is observed.

1.3.4 CRS-207 and Pembrolizumab, and Epacadostat Regimens

This is the first study to investigate the administration of CRS-207 with epacadostat and pembrolizumab. As of November 3, 2016, 8 subjects have been treated with CRS-207 in combination with epacadostat (4 subjects with 100mg BID epacadostat, and 4 subjects with 300mg BID epacadostat) in the Phase 1 portion of this study. No DLTs have been observed and the combination was well-tolerated at both dose levels tested.

CRS-207 is currently being evaluated with the PD-1 inhibitor nivolumab in an investigator-sponsored Phase 2 study in subjects with previously-treated pancreatic cancer (ADU-CL-06; NCT02243371). As of December 5, 2016, approximately 51 subjects have been treated with a combination that includes CRS-207 and nivolumab. Initial data from this ongoing clinical study suggests an acceptable tolerability profile of both agents at full dose (CRS-207 1×10^9 CFU with nivolumab at 3 mg/kg). Refer to the CRS-207 Investigators Brochure for additional information.

An ongoing study (INCB24360-202) with epacadostat and pembrolizumab showed that the combination was well-tolerated at all dose levels tested, including the 300mg BID dose of epacadostat.

Although there was a somewhat higher incidence of grade 3 rash observed in the 300 mg BID cohort compared to the 100 mg BID cohort, these events did not qualify as protocol-specified DLTs. A dose of 300 mg epacadostat in combination with pembrolizumab is currently being investigated in additional clinical studies.

In the aforementioned study (INCB24360-202), there was evidence of improved efficacy in melanoma subjects at all doses of epacadostat examined (50 to 300 mg BID). A Phase 3 study (INCB24360-301) is ongoing in subjects with unresectable or metastatic melanoma; in this study the dose of 100 mg bid epacadostat with pembrolizumab is based upon a benefit/risk assessment specific to the study population and indication. Given melanoma is considered responsive to

immunotherapy, and lower doses of epacadostat appeared to have similar activity, the 100 mg BID dose combination was selected to lower the potential of dose interruptions and dose reductions relative to a higher dose.

In other tumor types (including ovarian, peritoneal, and fallopian tube carcinomas), which may be less responsive to known immunotherapies, greater target coverage for inhibition of IDO1 may be necessary. PK/PD modelling suggests doses of 100 mg BID epacadostat achieve an average IC_{50} at trough in most subjects. At 300 mg BID, epacadostat achieves target inhibition above the IC_{90} at trough thereby shifting the benefit/risk in favor of the higher epacadostat dose for tumor types generally considered less responsive to immunotherapy.

For these reasons the proposed combinations in this study will be evaluated with Phase 1 dose evaluation and provision in Phase 2 to adjust the dose of epacadostat in the event of unacceptable toxicity following the addition of pembrolizumab to the CRS-207/IDO combination.

2 STUDY OBJECTIVES

2.1 Phase 1: Dose Evaluation, Assigned Arms

Objective(s)	Endpoints
Primary • Determine the RP2D of epacadostat administered with CRS-207 in subjects with platinum-resistant ovarian, fallopian or peritoneal cancer • Assess safety and tolerability of CRS-207 alone and CRS-207 in combination with epacadostat in subjects with platinum-resistant ovarian, fallopian or peritoneal cancer	**Primary** • Hematologic and non-hematologic DLTs; • Adverse events by CTCAE grade; vital signs, physical exam findings, changes in ECG readings and changes in chemistry and hematology and coagulation parameters
Secondary • Characterize the PK of epacadostat • Evaluate the preliminary anti-tumor activity of each study drug regimen • Characterize pharmacological effects on immune biomarkers in peripheral blood and tumor tissue • Characterize shedding and clearance of CRS-207 when given alone or with epacadostat	**Secondary** • Plasma concentration of epacadostat and derived PK parameters; • ORR, defined as CR or PR as determined by mRECIST, RECIST v1.1, and GCIG CA-125 criteria; • PFS, defined as the time from the date of first dose to PD or death due to any cause. PFS is measured through the last tumor assessment or commencement of a new systemic therapy. PD is determined by mRECIST, RECIST v1.1 and GCIG CA-125 criteria; • Disease control rate, defined as CR+PR+SD as determined by mRECIST, RECIST v1.1, and GCIG CA-125 criteria; • Duration of response, defined as the time from first CR or PR until PD as determined by mRECIST, RECIST v1.1, and GCIG CA-125 criteria; • OS, defined as the time from first dose until date of death due to any cause; • Ratio of tumor infiltrating lymphocytes CD8/T_{reg} (FoxP3); • Plasma kynurenine/tryptophan ratio; • Other immunological and tumor biomarker endpoints: o Cytokine/chemokine responses o Antibody responses o Modulation of immune cell populations and functions in PBMCs and tumor, and o CA-125, mesothelin, PD-L1 and additional tumor biomarkers; and • Detection of CRS-207 in urine, saliva, feces, and blood
CA-125 = cancer antigen-125; CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events; DLT = dose-limiting toxicity; GCIG = Gynecologic Cancer Intergroup; IDO = epacadostat; mRECIST = modified Response Evaluation Criteria in Solid Tumors; ORR = objective response rate; OS = overall survival; PBMC = peripheral blood mononuclear cells; PD = disease progression; PD-L1 = programmed death receptor ligand 1; pembro = pembrolizumab; PFS = progression-free survival; PK = pharmacokinetics; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended Phase 2 dose; SD = stable disease; T_{reg} = regulatory T cells.	

2.2 Phase 2: Randomized, 2-stage

Objective(s)	Endpoints
Primary • Assess safety of CRS-207/pembrolizumab administered with or without epacadostat • Assess tumor response and PFS	**Primary** • Adverse events, vital signs, physical exam findings, changes in ECG readings, and changes in chemistry, hematology, and coagulation parameters • ORR, defined as CR or PR as determined by mRECIST • PFS, defined as the time from the date of first dose to PD or death due to any cause. PFS is measured through the last tumor assessment or commencement of a new systemic therapy. PD is determined by mRECIST.
Secondary • Assess disease control rate and duration of response • Assess OS	**Secondary** • Disease control rate, defined as CR+PR+SD as determined by mRECIST, RECIST v1.1, and GCIG CA-125 criteria • Duration of response, defined as the time from first CR or PR until PD as determined by mRECIST, RECIST v1.1, and GCIG CA-125 criteria • ORR as determined by RECIST v1.1 and GCIG CA-125 criteria • OS, defined as the time from first dose until date of death due to any cause • PFS where PD is determined by RECIST v1.1 and GCIG CA-125 criteria
Additional • Assess the association of clinical efficacy (ORR, PFS, and OS) with immunologic and tumor biomarkers • Characterize the PK of epacadostat • Characterize shedding and clearance of CRS-207/pembrolizumab administered with or without epacadostat	**Additional** Immunological and tumor biomarker endpoints: • Cytokine/chemokine and antibody responses • Modulation of immune cell populations and functions in PBMCs and tumor • Mesothelin and PD-L1 expression • CA-125 and additional candidate tumor biomarkers Pharmacokinetic endpoints: • Plasma concentration of epacadostat and derived PK parameters • Detection of CRS-207 in urine, saliva, feces, and blood

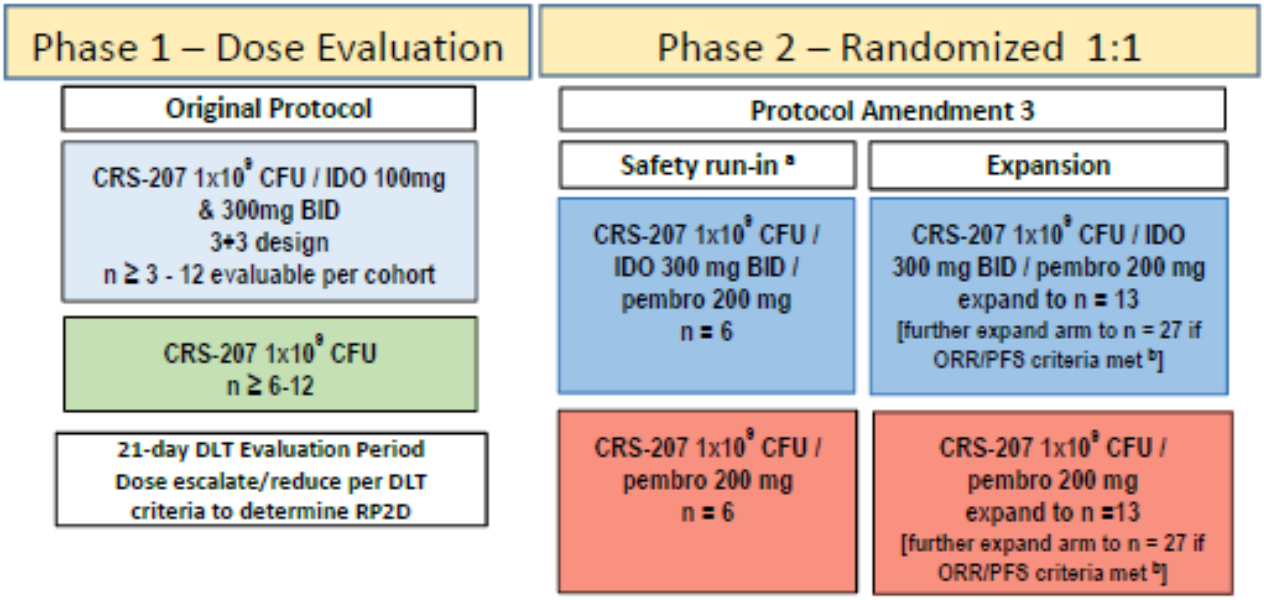
3 STUDY DESIGN

The study is designed to assess the safety and efficacy of the following investigational treatment regimens in adult females with epithelial ovarian, fallopian, or primary peritoneal cancer that is platinum-resistant (i.e. has progressed within 6 months after completing platinum-based chemotherapy):

- CRS-207/epacadostat/pembrolizumab (CRS-207/IDO/pembro)
- CRS-207/pembrolizumab (CRS-207/pembro)

The study will be conducted in 2 phases as depicted in the study schematic (Figure 1). Phase 1 seeks to evaluate safety and tolerability and is aimed at determining the recommended Phase 2 dose (RP2D) of epacadostat administered with CRS-207 for further evaluation in Phase 2. The randomized Phase 2 portion of the study will begin with a safety-run in to evaluate the addition of pembrolizumab, followed by a 2-stage design to evaluate safety and efficacy in subjects who have received no more than 3 prior chemotherapy regimens for locally advanced or metastatic disease.

Figure 1 Study Schematic



IDO = epacadostat

[a] A Safety Run-in will be completed at the RP2D for the first 12 randomized subjects (6 per arm). Treatment of the first 6 subjects in each arm will be staggered, with no more than 1 subject treated per arm, per week. Subjects will be monitored during the first 28 days (at least through 7 days after the Cycle 2 pembro/CRS-207 infusions). The SRC will review adverse events on an ongoing basis; in the event 2 or more subjects in the first 6 treated experience DLTs, the SRC will be convened to determine if a dose modification is required. If the phase 2 dose is modified, at least 13 subjects will be enrolled and treated at the final dose level.

[b] If ORR/PFS criteria are met, enrollment in that Arm is continued to n = 27. The ORR/PFS criteria are: Among the first 13 subjects (at the final dose level) $\geq$1 respond or median PFS $\geq$ 4.8 months.

The Schedules of Events for Phases 1 and 2 are provided in Appendix F and Table 1, respectively. The study consists of a 28-day screening period, followed by administration of study drug(s) in 3-week cycles. Treatment will continue for as long as there is adequate safety and potential for clinical benefit with the exception that pembrolizumab may be given for up to 24 months to subjects without disease progression. After 6 cycles, CRS-207 will be administered every 6 weeks (Q6W); all other assigned treatments remain the same.

Archived tumor tissue and paired tumor biopsies (collected at Screening and Cycle 2 Day 15) will be used to explore the association of programmed death receptor ligand-1 (PD-L1) expression, mesothelin expression, and tumor-infiltrating lymphocyte (TIL) characteristics with clinical responses. Tumor evaluation by radiographic imaging will be performed within 28 days prior to treatment and every 9 weeks while on treatment and until disease progression. Peripheral blood will be collected to assess immune responses directed against *L. monocytogenes*, mesothelin, and other tumor-associated antigens. Circulating levels of Cancer antigen 125 (CA-125) will be assessed at Screening and on Day 1 of each 3 week cycle while on treatment, and every 9 weeks thereafter until disease progression is confirmed. CRS-207 shedding and clearance will be assessed during Phase 1 and during the Safety Run-in of Phase 2 at US sites only. Urine, rectal swab, oral swab, and whole blood will be collected from subjects treated with CRS-207. Additional assessments will be performed if results are positive for CRS-207 at the Day 7 time point.

An End-of-Treatment (EOT) Visit will be scheduled once treatment has been discontinued. Blood will be collected at EOT to assess clearance of CRS-207 and at [redacted]. To eliminate any potentially residual CRS-207, subjects will be administered antibiotics at the EOT Visit; the antibiotic regimen should be completed prior to receiving any subsequent cancer-related therapy. An additional Safety Follow-up Visit will occur 30 days after the last dose of study drug. If the subject begins another anticancer therapy before the end of the 30-day period, the subject should complete all of the Safety Follow-up Visit assessments prior to commencing the new therapy.

After the Safety Follow-up Visit, subjects will return to the clinic every 9 weeks for tumor evaluation and CA-125 until radiographic disease progression is confirmed, at which time subjects will be followed every 12 weeks by phone/email (if no recent medical charting available) to collect data on survival and any subsequent anti-cancer treatment that may have been administered. Follow-up will continue until death, withdrawal of consent, or the end of the study, whichever occurs first. At the conclusion of the study, all remaining subjects who have received at least 1 dose of study treatment will be offered enrollment in a long-term follow-up study and continue to be followed for survival.

Additional guidelines specific to the Phase 1 and 2 portions of the study are provided below.

3.1 Phase 1: Dose Evaluation, Assigned Arms

The epacadostat dose will be evaluated based on a 3+3 design utilizing protocol defined DLT criteria (Table 2).

Table 2 Phase 1 Dose Evaluation Plan

Cohort[3]	0/3 subjects have DLT[1]	1/3 subjects have DLT[1]	<2/6 subjects have DLT[1]	≥2 in a cohort have DLT[1,2]
Dose Cohort 1 CRS-207 + 100 mg BID IDO	Escalate to Dose Cohort 2	Expand Dose Cohort 1 to 6 subjects	Escalate to Dose Cohort 2	De-escalate to Dose Cohort -1 (CRS-207 + 50 mg BID IDO)[3]
Dose Cohort 2 CRS-207 + 300 mg BID IDO	Expand cohort to 12 subjects with paired biopsies	Expand Dose Cohort 2 to 6 subjects	Expand cohort to 12 subjects with paired biopsies	Dose expand with 100 mg BID IDO

1. DLT period is 3 weeks after first dose of CRS-207.
2. In the case that a cohort is closed to enrollment, subjects who are ongoing at that dose level without DLTs may continue treatment at the assigned dose level at the discretion of the Investigator.
3. Evaluation of Dose Cohort -1 will enable the same 3+3 rules for dose cohort expansion or de-escalation to 25 mg (Dose Cohort -2). Evaluation of Dose Cohort -2 will enable the same 3+3 rules for dose cohort expansion. If Dose Cohort -2 is not tolerated, Treatment Arm will be terminated.

BID = twice daily; DLT = dose-limiting toxicity

Additionally, approximately 12 subjects with paired biopsies will be enrolled in the CRS-207 alone arm to assess the safety and tolerability of CRS-207 alone in subjects with platinum-resistant ovarian, fallopian or peritoneal cancer.

A Safety Review Committee (SRC) will be convened for the study, consisting of the Investigators who enrolled subjects in the study, the Lead Investigator, Study Medical Monitor, and Sponsor representatives. Adverse events, DLTs and safety data for all subjects will be reviewed on an ongoing basis by the SRC. Dose escalation and reduction decisions, determination of the recommended dose for expansion, and R2PD will be made by the SRC.

3.2 Phase 2: Randomized, 2-Stage

Phase 2 will begin by assessing safety the addition of pembrolizumab to CRS-207 and CRS-207/epacadostat; pembrolizumab will be administered at the 200 mg fixed dose level (as approved in other cancer indications). Phase 2 will initiate after the RP2D of CRS-207/epacadostat is determined and approximately 12 subjects with paired biopsies have been dosed at that level.

A Safety Run-in will be completed since there are no precedent data on the addition of pembrolizumab to the planned drug combinations. Treatment of the first 6 randomized subjects in each treatment arm will be staggered, with no more than 1 subject treated per week, per arm. Subjects will be monitored during the Safety Run-in Period [the first 21 days] using the protocol defined DLT criteria. In the event ≥2 subjects in up to 6 (per arm) experience DLTs, the SRC will convene to determine if subsequent subjects enrolled will require a different dose level (Table 3), or if additional subjects should be enrolled at a specified dose level to further assess safety and tolerability. In the event ≥2 subjects in the next 6 subjects (per arm) treated experience DLTs, the SRC will reconvene to determine if the dose will be further modified for the remaining subjects to be enrolled. The SRC may convene at any time during the Safety Run-in Period to review and evaluate available safety data as warranted by emerging safety data.

Table 3 Safety Run-in Dose Levels and Dose Reduction

Dose level	pembrolizumab	epacadostat	CRS-207
1	200 mg	300 mg BID	1×10^9 CFU
-1	200 mg	100 mg BID	1×10^9 CFU
-2	Further dose reductions will be discussed and confirmed by the SRC based on emergent safety data.		

Phase 2 will utilize a 2-stage design. Subjects will be randomized 1:1 into 2 treatment arms. In the first stage, once the final dose is confirmed in the Safety Run-in, a total of 13 subjects will be randomized into each arm (total 26 subjects). If the phase 2 dose is modified, at least 13 subjects will be enrolled and treated at the final dose level in each arm. If the pre-specified objective response-rate (ORR) and progression-free survival (PFS) criteria for advancement in the 2-stage design are met (≥1 response or median PFS ≥ 4.8 months) for an arm, an additional 14 subjects will be enrolled in that arm, for a potential total of 27 subjects per arm (up to 54 subjects total if both arms advance to stage 2).

In the event that during the safety run in there are 2 DLTs in 6 patients in the CRS-207/pembrolizumab arm but the CRS-207/pembrolizumab/epacadostat has 0 or 1 DLTs in 6 patients using the same dose levels as in the 2 arm combination, the SRC will review the data and may allow enrollment of another 3 subjects in each run-in to better define the toxicities.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

Individuals must meet all of the following requirements to be eligible to enroll in this study:

1. Female, 18 years of age or older
2. Histologically-confirmed disease

For Phase 1: Individuals with epithelial ovarian cancer, fallopian tube carcinoma, or primary peritoneal carcinomas who are considered to have platinum-resistant disease (defined as progression within 6 months from completion of platinum-based chemotherapy). The date should be calculated from the last administered dose of platinum therapy.

For Phase 2: Individuals with epithelial ovarian cancer, fallopian tube carcinoma, or primary peritoneal carcinomas who are considered to have platinum-resistant disease (defined as progression within 6 months from completion of a minimum of 4 platinum therapy cycles). The date should be calculated from the last administered dose of platinum therapy.

3. Measurable disease, as defined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

Phase 1 only: Individuals who do not have measurable disease (according to RECIST v1.1) but have assessable disease according to the Gynecologic Cancer Intergroup (GCIG) CA-125 criteria and require treatment, may be included if they meet all other criteria.

4. Agree to provide core tissue biopsies at baseline and at Cycle 2 Day 15
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
6. Available archived tumor tissue for central analysis
7. Adequate organ and marrow function, as defined by:
   - White blood cells ≥3000/μL
   - Absolute neutrophil count (ANC) ≥1500/μL
   - Absolute lymphocyte count ≥ 800/μL
   - Platelet count ≥100,000/μL
   - Serum albumin ≥3 g/dL
   - AST and ALT ≤2.5 × upper limit of normal (ULN) (<5 × ULN for subjects with liver metastases)
   - Total bilirubin ≤ the institutional ULN or conjugated bilirubin ≤ 1.2 × ULN (need only be tested if total bilirubin exceeds ULN) or ≤ 3 × institutional ULN if due to Gilbert's disease
   - Serum creatinine ≤1.5 × ULN or calculated creatinine clearance (CrCl) (estimated glomerular filtration rate [eGFR] can also be used in place of creatinine or CrCl) >50 mL/min for serum creatinine >1.5 × ULN
   - Hemoglobin ≥9 g/dL
   - International normalized ratio (INR) or prothrombin time (PT) ≤1.5 × ULN. Activated partial thromboplastin time (aPTT) ≤1.5 × ULN (unless receiving

anticoagulant therapy in which case values should be within therapeutic range of intended use)

Any other Grade 3 or higher lab abnormalities should be discussed and approved by the Study Medical Monitor prior to enrollment (even if not considered clinically significant)

8. Women of childbearing potential must agree to take appropriate precautions to avoid pregnancy, including the use of a medically acceptable method of highly effective contraception throughout the study and for 120 days after their final study drug administration. A barrier method of contraception must be employed regardless of other methods. Permitted methods that are at least 99% effective in preventing pregnancy should be communicated to the subject and their understanding confirmed.
9. Functional gastrointestinal tract (defined as no enterocutaneous fistulas and no proximal stomas). Individuals with a venting gastrostomy tube must be able to tolerate clamping for 2 hours following oral drug administration.
10. .Provides informed consent and is willing and able to comply with all study procedures.

4.2 Exclusion Criteria

Individuals who meet any of the following exclusion criteria will not be eligible to participate in the study:

1. Platinum-refractory disease (defined as progression during the first platinum-based chemotherapy)
2. Major surgical procedure within 4 weeks prior to dosing
3. Inaccessible tumors or for whom biopsy is contraindicated
4. Clinically significant ascites
5. **Phase 2 only**: Previous treatment with >3 chemotherapy regimens for locally advanced or metastatic disease
    - Repeat exposure to the same regimen separated in time by more than 3 months counts as 2 regimens
    - Regimens given as adjuvant therapy or as maintenance therapy after disease relapse are not included
    - Targeted agents will be included in the count
    - Bevacizumab will not count if administered as a single agent

    (There is no limit on the number of prior regimens for subjects entered into Phase 1)
6. Active bowel obstruction, or hospitalization for bowel obstruction within 2 months prior to screening
7. Requires parenteral nutrition or other agents aimed at improving performance status
8. Hospitalization within 2 weeks prior to screening

9. Received any anticancer medication or therapy in the 21 days prior to first dose of study drug or any unresolved toxicity > Grade 1 from previous anticancer therapy, except for stable chronic toxicities that are not expected to resolve (i.e. peripheral neurotoxicity, alopecia, fatigue, etc.). Palliative radiotherapy is allowed if completed at least 2 weeks prior to first dose of study treatment.
10. Prior monoclonal antibody treatment within 4 weeks before first dose of study drug, or not recovered (≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier
11. History of listeriosis or previous treatment with a *Listeria*-based immunotherapy
12. Known allergy to <u>both</u> penicillin and sulfa antibiotics
13. Any immunodeficiency disease or immune-compromised state (e.g. use of immunosuppressive agents) or had systemic steroids, TNF pathway inhibitors, or PI3 kinase inhibitors administered within 14 days prior to initiating study drug (use of inhaled or topical steroids or systemic corticosteroids <10 mg is permitted)
14. Received prior immune checkpoint inhibitors (e.g. anti-CTLA-4, anti-PD-1, anti-PD-L1, and any other antibody or drug specifically targeting T cell costimulation) or an IDO inhibitor. Individuals who have received experimental vaccines or other immunotherapies must obtain approval from the Study Medical Monitor to confirm eligibility.
15. Pregnant or breastfeeding; or intends to conceive a child from the start of screening through 120 days after the last dose of study drug
16. Clinically significant heart disease (such as unstable angina, myocardial infarction within 6 months of study initiation, congestive heart failure, or New York Heart Association Class III or IV heart failure, or arrhythmia requiring therapy)
17. Valvular heart disease that requires antibiotic prophylaxis for prevention of endocarditis, consistent with American Heart Association guidelines
18. History of any autoimmune disease which required systemic therapy in the past 2 years including but not limited to:
    - Inflammatory bowel disease (including ulcerative colitis and Crohn's Disease)
    - Rheumatoid arthritis
    - Systemic progressive sclerosis (scleroderma)
    - Systemic lupus erythematosus
    - Autoimmune vasculitis (e.g. Wegener's granulomatosis)
    - Central nervous system or motor neuropathy considered of autoimmune origin (e.g. Guillain-Barre Syndrome, Myasthenia gravis, multiple sclerosis)

    Individuals with vitiligo, Sjogren's Syndrome, interstitial cystitis, Graves' or Hashimoto's Disease, celiac disease, diabetes mellitus type 1, psoriasis, or hypothyroidism stable on hormone replacement will be allowed with Study Medical Monitor's approval

19. Diagnosed with another malignancy within the past 3 years (excluding a history of carcinoma in situ of the cervix, superficial non-melanoma skin cancer, superficial bladder cancer, or endometrial cancer that has been adequately treated)
20. Individuals with treated (surgically excised or irradiated) and stable brain metastases are eligible as long as the treatment was at least 4 weeks prior to initiation of study drug and baseline brain computed tomography (CT) with contrast or magnetic resonance imaging (MRI) within 2 weeks of initiation of study drug is negative for new brain metastases. Individuals with stable brain metastases must not require therapy with corticosteroids.
21. History of interstitial lung disease
22. Evidence of interstitial lung disease or active, noninfectious pneumonitis including symptomatic and/or pneumonitis requiring treatment
23. Active infection requiring systemic therapy
24. History of organ transplant that requires use of immunosuppressive therapy
25. Received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including G-CSF, GM-CSF or recombinant erythropoietin) within 4 weeks prior to first dose of study drug.
26. Intercurrent illness that is either life-threatening or of clinical significance such that it might limit compliance with study requirements
27. History of alcohol dependence or use of illicit drugs (e.g. opioids, cocaine, amphetamines, or hallucinogens) that could potentially interfere with adherence to study procedures or requirements
28. Received a diagnosis of human immunodeficiency virus or human T-lymphotropic virus, or has a known history of, or is positive for, Hepatitis B (HBsAg reactive) or Hepatitis C (HCV RNA [qualitative] is detected)
29. Received any prophylactic vaccine within 14 days of first dose of study drug or received a live vaccine within 30 days of first dose of study drug
30. Has 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 that were placed more than 3 months prior to first dose of study drug.
31. Known or suspected allergy or hypersensitivity to yeast or any other component of CRS-207 (e.g. glycerol); or known allergy or reaction to any component of epacadostat formulation; or any history of severe hypersensitivity reactions to pembrolizumab, its excipients or any monoclonal antibody therapy
32. Currently receiving therapy with a UDP-glucuronosyltransferase 1A9 (UGT1A9) inhibitor including diclofenac, imipramine, ketoconazole, mefenamic acid, and probenecid. Individual may enter screening if therapy is able to be discontinued (a 7 days washout period is required prior to first dose of epacadostat, or 5 half-lives have elapsed for the specific UGT1A9).

33. Presence of a gastrointestinal condition that may affect drug absorption
34. Receiving monoamine oxidase inhibitors (MAOIs) or a drug which has significant MAOI activity (meperidine, linezolid, methylene blue) within the 21 days before screening
35. Any history of Serotonin Syndrome after receiving serotonergic drugs
36. History or presence of an abnormal electrocardiogram (ECG) that, in the Investigator's opinion, is clinically meaningful. Screening QTcF interval >480 ms is excluded. In the event that a single QTcF is >480 ms, the subject may enroll if the average QTcF for the 3 ECGs is <480 ms. For subjects with an intraventricular conduction delay (QRS interval >120 ms), the JTc interval may be used in place of the QTcF with Sponsor approval. The JTc must be <340 ms if JTc is used in place of the QTcF. Individuals with an intraventricular delay due to a left bundle branch block are excluded.

    Note: QTcF prolongation due to pacemaker may enroll if the JTc is normal.
37. Uses more than 4 g/day of acetaminophen
38. Has an unhealed surgical wound
39. Insufficient peripheral venous access to permit completion of the study dosing and compliance with study phlebotomy regimen
40. Participated in any other study in which receipt of an investigational new drug occurred within 28 days of first dose of study drug
41. Unwilling or unable to follow the study schedule for any reason.

4.3 Dose Eligibility

4.3.1 CRS-207

Subjects must have adequate organ function as defined by the laboratory values in Table 4 prior to each dosing cycle where CRS-207 is administered. The Study Medical Monitor will be notified of any dose delays due to safety concerns (eg if the subject is recovering from an AE or pembrolizumab infusion reaction) and to discuss a plan to resume treatment. If a dose is delayed beyond 7 days post pembrolizumab, the dose of CRS-207 should be withheld until the next Cycle. If dose is delayed more than 2 weeks, contact the Medical Monitor for further instruction on continued dosing.

Table 4 Dosing Eligibility Requirements for CRS-207

Hematologic	Renal	Hepatic
WBC ≥3000/μL ANC ≥1000/μL Platelets ≥100,000/μL Hemoglobin ≥8 g/dL	Creatinine ≤1.5 × ULN	AST/ALT ≤ 5 × ULN Bilirubin ≤ 1.5 × ULN OR ≤ 3 × ULN if due to Gilbert's disease
ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ULN = upper limit of normal; WBC = white blood cell.		

4.3.2 Epacadostat and Pembrolizumab

If the subject meets eligibility criteria for the study and is assigned or randomized to receive epacadostat BID and/or pembrolizumab, dosing may initiate and should continue per protocol. The Study Medical Monitor will be notified of any dose interruptions due to safety concerns (Section 5.4.1).

Pembrolizumab dosing may be delayed up to 2 weeks, after which time it will be considered missed and the subject would continue onto the next scheduled dose. If a dose is delayed more than 2 weeks, contact the Sponsor Medical Monitor for further instruction on continued dosing.

4.4 Subject Discontinuation

A subject may be removed from treatment for any of the following reasons:

- Occurrence of an adverse event that presents an unacceptable consequence or risk to the subject
- Subject has received treatment, and there is no longer potential for clinical benefit (treatment should continue beyond initial progression of disease if there is potential for clinical benefit)
- Noncompliance (failure to receive clinical study medication or treatment as mandated by the protocol, or failure to comply with protocol requirements)
- A subject becoming pregnant while on study drug
- Consent is withdrawn by the subject or legal representative
- Study is discontinued by the Sponsor

If a subject provides a baseline biopsy and then subsequently a second biopsy at Cycle 2 Day 15 cannot be obtained due to safety or accessibility issues then the subject may remain on study treatment if they do not otherwise meet the criteria for withdrawal.

Subjects may withdraw consent or discontinue from the study at any time for any reason. Every effort will be made to follow all subjects for PD and survival. If a subject withdraws prematurely from the study due to the above criteria or any other reason, study staff should make every effort to complete the full panel of assessments scheduled for the EOT and Safety Follow-up visits including the post-treatment monitoring for CRS-207. If the EOT Visit occurs >21 days after the last administration of study drug, procedures from the EOT and Safety Follow-up visits may be collected as a single Safety Follow-up Visit. The reason for subject withdrawal must be documented in the electronic Case Report Form (eCRF).

In the case of subjects lost to follow-up, attempts to contact the subject must be made and documented in the subject's study records. Sites will attempt to obtain vital status data (e.g. death or last date known alive) from public records or other external sources where possible if a subject withdraws consent from study (i.e. refuse follow-up for vital status) or is documented as lost to follow up.

5 STUDY TREATMENTS

5.1 Treatment Arms

Subjects will be assigned or randomized to the following treatment arms described in Table 5.

Table 5 ADU-CL-11 Treatment Cycles by Arm

Phase	Arm	Dose [1] / Route	Treatment Cycle
1	CRS-207	CRS-207: 1×10^9 CFU by IV infusion over ~ 1 hour	CRS-207: Day 1 of each cycle (Cycles 1-6); Q6W thereafter
1	CRS-207/ IDO	CRS-207: 1×10^9 CFU by IV infusion over ~ 1 hour IDO: 100 mg or 300 mg BID Oral	CRS-207: Day 1 of each cycle (Cycles 1-6); Q6W thereafter IDO: BID starting Cycle 1 Day 2
2	CRS-207/ Pembro/ IDO	Pembro: 200 mg by IV infusion over 30 min CRS-207: 1×10^9 CFU by IV infusion over ~ 1 hour IDO: 300 mg Oral BID [1]	Pembro: Day 1 of each cycle CRS-207: Day 2 of each cycle (Cycles 1-6); Q6W thereafter IDO: BID starting Cycle 1 Day 3
2	CRS-207/ Pembro	Pembro: 200 mg by IV infusion over 30 min CRS-207: 1×10^9 CFU by IV infusion over ~ 1 hour	Pembro: Day 1 of each cycle CRS-207: Day 2 of each cycle (Cycles 1-6); Q6W thereafter

BID = twice daily; CFU = colony-forming units; IDO = epacadostat; IV = intravenous; pembro = pembrolizumab; Q6W = once every 6 weeks
[1] RP2D of epacadostat based on Phase 1 dose-evaluation parameters and determined by the SRC; the Phase 2 dose may be further adjusted during Phase 2 Safety Run-in

5.2 Treatment Assignment

Phase 1 of the study will be open-label and subjects will be assigned to Arms as specified in the study design (Section 3.1).

Phase 2 of the study will be open-label and randomized. Subjects (including subjects enrolled in Safety Run-in) will be randomized in a 1:1 manner to receive CRS-207/ epacadostat/pembrolizumab or CRS-207/pembrolizumab.

5.3 Dose Limiting Toxicities

During Phase 1, the DLT evaluation period is defined as Cycle 1 (21 days).

During the Phase 2 Safety Run-in, the DLT evaluation period is defined as Cycle 1 (the first 21 days).

5.3.1 Non-Hematologic Events

For non-hematological events, a DLT is defined as any treatment-emergent adverse event (TEAE) not attributable to disease or disease-related processes that occurs during the DLT observation period (Cycle 1) and is Grade 3 or higher according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.

In addition, any use of systemic steroids or a study drug dose interruption lasting more than 7 days for an adverse event with an unclear relationship to study drug will be considered a DLT even if the other DLT criteria are not fulfilled.

The following non-hematological adverse events are NOT considered DLTs:

- Grade 3 aspartate aminotransferase (AST), alanine aminotransferase (ALT), or alkaline phosphatase levels persisting for <7 days;
- Grade 3 fatigue lasting <3 days;
- Grade 3 nausea or vomiting that has resolved to ≤ Grade 2 within 48 hours with standard antiemetic therapies;
- Grade 3 diarrhea that has resolved to ≤ Grade 2 within 48 hours with standard antidiarrheal therapies;
- Grade 3 fever;
- Grade 3 or 4 laboratory finding that is asymptomatic and rapidly reversible (returned to baseline or ≤ Grade 1 within 7 days) unless identified as clinically significant by the Investigator;
- Any Grade 3 or lower change in cholesterol or triglycerides or asymptomatic change in lipid profile; and/or
- Singular or non-fasting elevations in blood glucose (i.e. blood glucose excursions will be considered a DLT if fasting blood glucose is elevated (Grade 3 or higher) on 2 separate occasions).

5.3.2 Hematologic Events

For hematologic events, a DLT is defined as follows:

- Grade 4 neutropenia lasting >7 days;
- Grade ≥3 febrile neutropenia;
- Grade 4 anemia;
- Grade 4 thrombocytopenia or ≥ Grade 3 thrombocytopenia lasting >7 days or associated with bleeding; and/or
- Dose delay >7 days secondary to myelosuppression.

Toxicities will be monitored throughout the study, and if the toxicity levels in any Arm are unacceptable (>33% of subjects), then dosing will be suspended until further review and consideration by the SRC.

5.4 Other Adverse Event Considerations

5.4.1 Dose Interruption, Modification, and Management of Events Associated with Study Treatments

In some circumstances, it may be necessary to temporarily interrupt one or more study treatments as a result of adverse events that may have an unclear relationship to study drug.

Any interruptions of >2 weeks or for LFT abnormalities must be discussed with the Study Medical Monitor before resuming treatment. Treatment with all study drugs should be withheld for drug-related Grade 4 hematologic toxicities, nonhematological toxicity ≥ Grade 3 (including laboratory abnormalities), and severe or life-threatening adverse events.

Except in cases of emergency, it is recommended that the Investigator consult with the Study Medical Monitor (or other representative of the Sponsor) before temporarily interrupting therapy for reasons other than protocol-mandated medication hold. Additionally, the Investigator must notify the Study Medical Monitor and Study Project Manager via email before restarting study drug that was temporarily interrupted because of an adverse event.

Dosing interruptions may be permitted in the case of medical/surgical events or logistical reasons not related to study therapy (e.g. elective surgery, unrelated medical events, vacation, and/or holidays) upon review and approval from the Study Medical Monitor. Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the sponsor. The reason for interruption should be documented in the subject's study record. Pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons. CRS-207 must be administered one day after pembrolizumab administration.

5.4.2 Criteria and Procedures for Dose Modification

CRS-207 has been well tolerated to date. The major safety signals have been infusion related reactions (Section 5.5.2.1). If a dose reduction of CRS-207 is being considered then the Study Medical Monitor should be contacted for further discussion.

Epacadostat dose may be reduced according to the guidelines and dose levels described in Table 6. Additional information related to dose changes for epacadostat for specific adverse events can be found in Section 5.4.3.3 for immune-related Adverse Events (irAEs) and Section 5.4.6 for an adverse event of SS. Dose modifications for pembrolizumab-related events are provided in Table 7.

If the subject experiences a new TEAE or is recovering from a TEAE, CRS-207 administration may be delayed up to 7 days following pembrolizumab administration; the Sponsor must be notified. If a dose of CRS-207 is delayed beyond 7 days of pembrolizumab, the dose of CRS-207 should be withheld until the next cycle.

Table 6 Dose Modification Guidance for Epacadostat

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Dose Level for Restarting Treatment	Treatment Discontinuation
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1	**Related**: Reduce by 1 dose level **Not Related**: 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
	4	Permanently discontinue	n/a	Permanently discontinue
AST, ALT, or Increased Bilirubin[1]	2	Toxicity resolves to Grade 0-1	**Related**: Reduce by 1 dose level **Not Related**: Same dose level	Toxicity does not resolve within 12 weeks of last dose
	3-4	Permanently discontinue (see exception below)[2]	n/a	Permanently discontinue
Type 1 diabetes mellitus (if new onset)	T1DM	Hold epacadostat for new onset Type 1 diabetes mellitus. Resume epacadostat when subjects are clinically and metabolically stable.	**Related**: Reduce by 1 dose level **Not Related**: Same dose level	Resume epacadostat when subjects are clinically and metabolically stable
Hyperglycemia	3-4	Hold epacadostat for Grade 3-4 hyperglycemia associated with evidence of beta cell failure. Resume epacadostat when subjects are clinically and metabolically stable.	**Related**: Reduce by 1 dose level **Not Related**: Same dose level	Resume epacadostat when subjects are clinically and metabolically stable
Hypophysitis	2-4	Therapy with epacadostat can be continued while endocrine replacement therapy is instituted.	**Related**: Reduce by 1 dose level **Not Related**: 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
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	**Related**: Reduce by 1 dose level **Not Related**: 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
	4	Permanently discontinue	n/a	Permanently discontinue
Hypothyroidism	1-4	Therapy with epacadostat can be continued while thyroid replacement therapy is instituted	n/a	Therapy with epacadostat can be continued while thyroid replacement therapy is instituted
Pneumonitis	2	Toxicity resolves to Grade 0-1	**Related**: Reduce by 1 dose level	

[1] Subjects with bone metastasis related elevations at baseline, contact sponsor to discuss clinical management and possible dose reductions of epacadostat.

[2] For subjects with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then subjects should be discontinued. For subjects have transient Grade 3 AST/ALT levels persisting for < 7 days and do NOT require steroids, epacadostat may reduce by 1 dose level once AST/ALT returns to baseline.

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Dose Level for Restarting Treatment	Treatment Discontinuation
			Not Related: 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
	3-4	Permanently discontinue	n/a	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	**Related**: Reduce by 1 dose level **Not Related**: 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
	3-4	Permanently discontinue	n/a	Permanently discontinue
All Other Drug-Related Toxicity	3 or Severe[3]	Toxicity resolves to Grade 0-1	**Related**: Reduce by 1 dose level **Not Related**: 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
	4	Permanently discontinue	n/a	Permanently discontinue

[3] Subjects with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue epacadostat 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.

Table 7 Pembrolizumab Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1	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
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose
	3-4	Permanently discontinue (see exception below)[a]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure	Resume pembrolizumab when subjects are clinically and metabolically stable
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	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
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	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
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted
Infusion Reaction	2[b]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	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
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	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
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[c]	3 or Severe	Toxicity resolves to Grade 0-1	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
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 (Grade 2 for pneumonitis) drug-related AE that recurs or any life-threatening event.

[a] For subjects with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then subjects should be discontinued. Grade 3 AST/ALT levels persisting for < 7 days, pembrolizumab may resume once AST/ALT has returns to baseline.

[b] If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be pre-medicated for the next scheduled dose; Refer to Table 9 for further management details.

[c] Subjects 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.

5.4.3 Immune-related Adverse Events

Subjects who develop an adverse event thought to be immune-related should have additional testing to rule out other etiologic causes. If laboratory results or symptoms indicate a possible

irAEs, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

5.4.3.1 Procedures and Supportive Care Guidelines for Subjects Exhibiting Immune-Related Adverse Events

The treatment guidelines outlined in this section are intended to guide the Investigator if the events are deemed related to epacadostat or pembrolizumab. The Study Medical Monitor is available to discuss procedures for treating subjects exhibiting irAEs.

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. 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.

IV systemic antibiotic treatment in order to ensure clearance of CRS-207 should be administered prior to initiation of systemic steroids required to treat suspected irAEs. However systemic steroids can be administered at the same time as systemic antibiotics if necessary due to the subject's condition.

- **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** and **Grade 4 events**, immediately treat with IV 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 gastrointestinal consultation and endoscopy to confirm or rule out colitis.
    - For **Grade 2 diarrhea/colitis** that persists >3 days, administer oral corticosteroids.
    - For **Grade 3 or 4 diarrhea/colitis** that persists >1 week, treat with IV 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 (T1DM) (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** and **Grade 4** Hyperglycemia:
        - Insulin replacement therapy is recommended for T1DM and for Grade 3 and Grade 4 hyperglycemia associated with metabolic acidosis or ketonuria.
        - Evaluate subjects 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** and **Grade 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 subjects 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** to **Grade 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 liothyroinine, is indicated per standard of care.
    - **Grade 3** and **Grade 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 LFTs more frequently until returned to baseline values (consider weekly or twice weekly if steroids are not initiated).
        - Treat with IV or oral corticosteroids.
    - For **Grade 3** and **Grade 4** events, treat with IV 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.

- **Renal Failure or Nephritis:**
  - For **Grade 2** events, treat with corticosteroids.
  - For **Grade 3** and **Grade 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.

5.4.3.2 Procedures for other Severe Immune-Mediated Adverse Reactions, Including Ocular Manifestations

All study drugs should be permanently discontinued for severe (Grade 4) irAEs. Systemic corticosteroid treatment should be initiated at a dose of 1 to 2 mg/kg per day of prednisone or equivalent for severe irAEs.

Corticosteroid eye drops should be administered to subjects who develop uveitis, iritis, or episcleritis. Epacadostat should be permanently discontinued for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy.

5.4.3.3 Discontinuation Rules and Procedures for Immune-Related Adverse Events

Adverse events of a potential immunologic etiology or irAEs may be defined as an adverse event of unknown etiology, associated with drug exposure and consistent with an immune phenomenon. IrAEs may be predicted based on the nature of the compounds, their mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to adverse events that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment.

If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes prior to labeling an adverse event as an irAE. If other causes exist, additional supportive care may be required.Subjects who develop a ≥ Grade 2 irAE should be discussed immediately with the Sponsor.

General supportive care recommendations to manage irAEs due to epacadostat are detailed in Table 8. In addition, recommendations for prophylactic and supportive care measures of specific irAEs, infusion reactions, pneumonitis, hepatitis, dermatitis, immune-mediated neuropathies, immune-mediated endocrinopathies, and ocular manifestations are detailed throughout Section 5.4.

irAEs may be attributable to one or more study drugs. If the event is clearly related to one of the agents, follow the instructions specific for that agent, if available. If the event is related to multiple agents, follow the action taken instructions provided, or consult the Study Medical Monitor.

Table 8 General Guidelines for Immune-Related Adverse Events Due to Epacadostat

irAE Toxicity Grade	Withhold/Discontinue Epacadostat*	Action Taken With Respect to Epacadostat	Supportive Care
Grade 1	No action.	Not applicable.	Provide symptomatic treatment.
Grade 2	May withhold epacadostat per Investigator's discretion.	May return to treatment if improves to Grade 1 or resolves within 6 weeks. If adverse event resolves within 4 weeks, subject may restart at the same dose and schedule for epacadostat. For an adverse event that does not resolve within 4 weeks, epacadostat should be reduced 1 dose level. If adverse event does not resolve within 6 weeks, study treatment with epacadostat should be discontinued or discussed with Study Medical Monitor.	Consider systemic corticosteroids in addition to appropriate symptomatic treatment.
Grade 3	Withhold or discontinue epacadostat. Discontinue if unable to reduce corticosteroid dose to <10 mg/day of prednisone or equivalent within 6 weeks of toxicity.	Any restart of study treatment must be discussed with Study Medical Monitor prior to restarting treatment.	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May use 1 to 2 mg/kg prednisone or equivalent per day. Steroid taper should be considered once symptoms improve to ≤ Grade 1 and tapered over at least 4 weeks in most cases.
Grade 4	Discontinue epacadostat.	Not applicable. Any exceptions require Study Medical Monitor approval.	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May use 1 to 2 mg/kg prednisone or equivalent per day. Steroid taper should be considered once symptoms improve to ≤ Grade 1 and tapered over at least 4 weeks in most cases.

irAE = immune-related adverse event.
*in any of the above scenarios where epacadostat is held or discontinued, contact the Study Medical Monitor for guidance on continuation of CRS-207 treatment.

Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

5.4.4 Management of Infusion Reactions Associated with Pembrolizumab

Signs and symptoms usually develop during or shortly after pembrolizumab infusion and generally resolve completely within 24 hours of completion of infusion. Table 9 shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab. The Study Medical Monitor will be consulted regarding continued dosing of CRS-207 and/or epacadostat should any of the events listed in Table 9 occur.

Table 9 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 trial treatment administration.**	Subject may be premedicated 1.5h (± 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).
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 (e.g., renal impairment, pulmonary infiltrates) 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 trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.4.5 Supportive Care

Subjects should receive appropriate supportive care measures as deemed necessary by the treating Investigator, including, but not limited to, the items outlined below:

- Nausea/vomiting: nausea and vomiting should be treated aggressively, and prophylactic antiemetic therapy should be used according to standard institutional practice. If a subject requires daily administration of an antiemetic, an alternative to dexamethasone should be used. Subjects should be strongly encouraged to maintain liberal oral fluid intake.

5.4.6 Procedures for Subjects Exhibiting Serotonin Syndrome

As noted in Section 1.3.4, there is a theoretical chance that epacadostat could cause an increase in serotonin levels in the brain that might trigger SS when administered in combination with other serotonergic agents.[60] This syndrome has been most closely associated with use of MAOIs, Demerol®, linezolid, or methylene blue; all of these agents are prohibited during the study (see Appendix D for prohibited medications associated with MAO inhibition). SSRIs and serotonin/norepinephrine reuptake inhibitors (SNRIs) are permitted in the study. Subjects will be provided with an informative subject leaflet describing the signs and symptoms of the syndrome along with instructions to seek immediate medical care if any of these signs or symptoms are observed. The following procedures will be implemented if subjects exhibit the signs/symptoms of SS described in Table 10, including tremor; hyperreflexia; and spontaneous, ocular, or inducible clonus, together with agitation, fever, diaphoresis, or muscle rigidity:

- Immediately interrupt all study drug administration;
- Immediately interrupt any SSRI or SNRI administration;
- Provide appropriate medical management of the subject until all signs/symptoms are resolved (e.g. IV fluids and/or sympathomimetic amines for hypotension, benzodiazepines for agitation, administration of 5-hydroxytryptamine antagonists such as cyproheptadine);
- If subject chooses to remain in the study, restart treatment with epacadostat after the SSRI or SNRI has been discontinued, no sooner than 5 half-lives have elapsed for the specific SSRI or SNRI in question, and after resolution of signs/symptoms of SS. The SSRI or SNRI treatment MAY NOT be restarted; and
- If subject chooses to withdraw from the study or must restart treatment with SSRI or SNRI, the subject should be scheduled for a follow-up visit. Treatment with SSRI or SNRI may be initiated 2 weeks after resolution of signs and symptoms of SS.

Table 10 Signs and Symptoms of Serotonin Syndrome

Tremor and hyperreflexia
Spontaneous clonus
Muscle rigidity, temperature >38°C (100.4°F), and either ocular clonus or inducible clonus
Ocular clonus and either agitation or diaphoresis
Inducible clonus and either agitation or diaphoresis

5.5 Drug Supplies

5.5.1 Formulation, Packaging, Preparation, and Dispensing

5.5.1.1 CRS-207

CRS-207 is a formulated live-attenuated strain hMeso38 of *Lm*, derived by deletion of *actA* and *inlB* coding sequences from a Streptomycin-resistant, wild-type strain and insertion of the hMeso coding sequence. The CRS-207 drug product consists of attenuated *Lm* (1×10^9 CFU total)

suspended in [redacted]. The drug product is filled at a volume of 1.5 mL into a single-use 2R injection glass vials with a gray butyl stopper and aluminum crimp seal with a flip-off cap, and stored frozen at -60ºC or colder until IV administration. CRS-207 is supplied by Aduro Biotech.

5.5.1.2 Epacadostat

Epacadostat (INCB024360) is formulated as an immediate release tablet. For this study, 25 mg and 100 mg tablets will be available. [redacted]

Epacadostat will be packaged in high-density polyethylene bottles of 35 tablets. Bottles will be labeled in the local language, and will comply with the legal and regulatory requirements of each country.

Epacadostat tablets will be dispensed on Day 1 of each indicated cycle in a sufficient amount required for the period of time until the next visit. Subjects will be provided a dosing diary and instructed to record each study drug dosing. Subjects will be instructed to return all unused study drug at the next visit.

Epacadostat is supplied by Incyte Corporation.

5.5.1.3 Pembrolizumab

Pembrolizumab, a humanized monoclonal antibody, is formulated and supplied as either a lyophilized powder or solution.

Pembrolizumab for injection is a sterile, preservative-free, white to off-white lyophilized powder in single-use vials. Each vial is reconstituted and diluted for intravenous infusion. Each 2 mL of reconstituted solution contains 50 mg of pembrolizumab and is formulated in L-histidine (3.1 mg), polysorbate 80 (0.4 mg), and sucrose (140 mg). May contain hydrochloric acid/sodium hydroxide to adjust pH to 5.5.

Pembrolizumab for injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for IV infusion. Each vial contains 100 mg of pembrolizumab in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, USP.

5.5.2 Study Drug Administration

5.5.2.1 CRS-207

CRS-207 is intended for administration by IV infusion (no in-line IV filter should be used). Additional details for storage and preparation of CRS-207 are provided in the study Pharmacy Manual.

Use of Central Lines:

To avoid contamination of a central line (e.g. infusion ports, peripherally inserted central catheter lines) with CRS-207 during and after infusion:

- **CRS-207 must NOT be administered through a central line or infusion ports;**
- **Central lines must NOT be used or accessed for any reason once the CRS-207 infusion has been initiated (including blood draws, medication administration, or line flushing; blood draws prior to infusion through a port or central line are allowed) and through 4 days after infusion;**
- **Central lines must be clearly labeled with tape or other method indicating the date when the port may be used again after CRS-207 infusion.**

Pre-Medication and Post-Infusion Observation

Before each CRS-207 infusion, subjects should be pre-medicated with 650 mg (or the maximum dose permitted by label) acetaminophen (paracetamol). Subjects allergic to acetaminophen may receive 800 mg ibuprofen. All subjects are required to receive a minimum of 500 mL of normal saline immediately before CRS-207 infusion; an additional 0.5 - 1 L after infusion is recommended, as tolerated. Additional fluids may be given for persistent tachycardia, fever, or hypotension based on Investigator's discretion.

Subjects will be observed in the clinic for at least 4 hours after the first CRS-207 infusion and at least 2 hours following each subsequent infusion. Subjects should continue to be monitored after infusion and released once they are considered clinically stable. Vital signs (blood pressure [BP], pulse, respiratory rate, temperature) will be obtained every 30 minutes during the CRS-207 infusion and every hour during post-infusion follow-up. Presence of fever alone does not preclude the subject from being released. Hospital admissions for overnight monitoring will not be considered an SAE unless the event meets criteria for seriousness other than hospitalization.

Accumulating subject experience during and after CRS-207 infusions at 1×10^9 CFU has further demonstrated the following clinical observations, which are to be expected:

- **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) can be used in alternate sequence every 4 hours. Rarely, a cooling blanket has been used during the clinic stay. Fevers after 24 hours are uncommon and rare after 36 hours.
- **Rigors:** Rigors/chills have been observed starting during or at the end of the CRS-207 infusion through 24 hours. IV narcotics such as morphine (use of meperidine is prohibited per protocol) can be administered per institutional policy.

- **BP:** Small drops in BP have been observed necessitating additional IV fluids during the 4 hour observation period (up to 1 or 2 L). Reasons for this include the development of may experience 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 on Day 2. Subjects are encouraged to hydrate themselves liberally at home with oral fluids.
- **Appetite:** Appetite is generally suppressed during the 24 hours after CRS-207 infusion related to the factors listed above. Liberal intake of fluids is encouraged.
- **Nausea** and vomiting**:** Nausea and vomiting have been reported and observed infrequently within 24 hours after CRS-207 infusion.

For more information, Refer to Section 5.6.1 and the IB for additional details on CRS-207 administration and supportive care.

5.5.2.2 Epacadostat

Subjects will take their dose of epacadostat in the morning and evening, approximately 12 hours apart without respect to food. If a dose is missed by more than 4 hours, that dose should be skipped and should be resumed at the scheduled time. Subjects will self-administer epacadostat except as specified in the Schedule of Events, when the morning dose will be given at the study site clinic.

5.5.2.3 Pembrolizumab

Pembrolizumab will be diluted and administered as a dose of 200 mg using a 30-minute IV infusion. Sites should target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps, a window between -5 minutes and +10 minutes is permitted (i.e. infusion time is 30 minutes -5 min/+10 min). Do not co-administer other drugs through the same infusion line. Pembrolizumab infusions will be administered Q3W for up to 24 months. The instruction for use contains specific instructions for the preparation of the pembrolizumab infusion and administration of infusion solution.

5.5.3 Treatment Compliance

All study drugs will be administered only to subjects participating in the study and complying with the instructions from the Investigator.

CRS-207 and pembrolizumab will be administered only by study personnel.

Compliance to the epacadostat study drug regimen will be evaluated by counting unused epacadostat tablets and reviewing the dosing diary. The objective is 100% compliance, and Investigators and their staff should evaluate compliance at each visit and take appropriate steps to optimize compliance. During the active treatment period, if compliance is not between 80% and 120%, inclusive, the subject will be counseled about the importance of compliance to the regimen. If outside these limits at 2 consecutive visits, the subject will be withdrawn from the study unless there is a sound reason for the compliance deviation.

5.5.4 Investigational Product Storage

5.5.4.1 CRS-207

CRS-207 must be stored at -60ºC or colder until just before use.

CRS-207 Environmental Precautions

In wild-type form, *Lm* is a bacterium commonly found in soil and water, and may be present in a variety of raw and processed foods. Listeriosis is a foodborne illness caused by wild-type *Lm* which primarily affects pregnant women and immunocompromised individuals. Direct human-to-human spread of *Lm* is believed to be limited mainly to vertical transmission from mother to neonate. CRS-207 is a LADD construct originating from wild-type *Lm* which contains deletions of 2 virulence genes that render it greater than 1000-times less toxic than wild-type *Lm* in mice.[28]

LADD-based immunotherapies (*Lm* Δ*actA*/Δ*inlB*), including CRS-207, have been designated as Risk Group 1 by the Aduro Institutional Biosafety Committee. Risk Group 1 is consistent with the guidance by the German ZKBS (Central Commission for Biological Safety) for classification of *Lm* strains with deletion in genes *prFA*, *hly*, *actA*, and *plcB*.[62] Individuals who prepare CRS-207 for infusion must take appropriate precautions (e.g. gloves, laboratory coat, face protection, needle stick or sharps precautions) to avoid contamination or direct contact with the agent. Once prepared for infusion, the chance for direct exposure to CRS-207 by study personnel should be greatly diminished. However, study personnel and staff should continue to adhere to the institutional guidelines for standard precautions.

Based on nonclinical studies and available clearance and shedding data from clinical studies, a subject who receives CRS-207 is unlikely to spread an infection to others. Subjects receiving CRS-207 should be counseled to minimize the potential risk of spreading CRS-207 by practicing good health hygiene (e.g. hand-washing) as with any potential infectious agent, and adhering to protocol requirements for barrier method of contraception during sexual intercourse.

5.5.4.2 Epacadostat

Epacadostat drug product should be stored at ambient conditions (15°C to 30°C).

5.5.4.3 Pembrolizumab

Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. If supplied as solution, do not freeze or shake.

5.5.5 Investigational Product Accountability

The Investigator is responsible for the control of investigational products under study. The investigational product must be used only in accordance with the Protocol. An investigational product dispensing log for CRS-207. epacadostat, and pembrolizumab must be kept current and should contain the following information:

- Delivery of study drug to the study site,
- Inventory of study drug at the site,
- The date and quantity of investigational products administered (including pill or vial counts from each supply dispensed [epacadostat] and/or administered [CRS-207, pembrolizumab]) to the subject,

- Return of study drug to the Investigator or designee by subjects (for epacadostat),
- Documentation of proper disposal of used investigational product, and
- Documentation of proper disposal (or return, at Sponsor's request) of unused investigational product.

Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities. At sites where destruction of the study drug is required before monitor inspection, the monitors rely on documentation of destruction per the site Standard Operating Procedures to verify drug accountability.

CRS-207 and Pembrolizumab

The investigational sites, per institutional guidelines, will destroy used CRS-207 and pembrolizumab vials after formulation for administration. The formulation of CRS-207 and pembrolizumab for administration and the destruction of each used vial will be carefully documented in the study Pharmacy Manual. Unused CRS-207 and pembrolizumab will be destroyed at the study site after final investigational product accountability and notification by Sponsor, unless otherwise directed by Sponsor or if Sites Drug Destruction SOPs requires return to the Study Sponsor.

Epacadostat

The Investigator or designee will be expected to collect and retain all used, unused, and partially used containers of epacadostat until verified by the study monitor (unless otherwise agreed to by the Sponsor). At the conclusion of the study, the Investigator or designee will oversee shipment of any remaining epacadostat back to the Sponsor or its designee for destruction according to institutional Standard Operating Procedures. If local procedures mandate on-site destruction of investigational supply, the site should (where local procedures allow) maintain the investigational supply until the study monitor inspects the accountability records in order to evaluate compliance and accuracy of accountability by the investigative site.

5.6 Prior and Concomitant Medications and/or Procedures

5.6.1 Permitted Medications and/or Procedures

During the course of the clinical study, subjects are anticipated to continue the use of prescribed medications identified during the screening procedures, consistent with study inclusion and exclusion criteria. Permitted concomitant medications used in this study include:

- 7-day antibiotic regimen scheduled 7 days after the last dose of CRS-207 (Section 5.6.3)
- Acetaminophen (paracetamol; ibuprofen if allergic to acetaminophen) prior to each CRS-207 infusion (no more than 4 g/d of acetaminophen)
- Antipyretics to treat fever or to prevent recurrence of fever
- Antiemetics according to American Society for Clinical Oncology guidelines.[63] If daily administration of an antiemetic is required, an alternative to dexamethasone should be used.
- IV narcotics such as morphine (per institutional policy) for rigors associated with CRS-207 dosing (use of meperidine is prohibited per protocol).

- Palliative (limited-field) radiation therapy is permitted for all anatomic sites except lung, but only for pain control to sites present at baseline and with approval by the Study Medical Monitor.

5.6.2 Restricted Medications and/or Procedures

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

- Non-study chemotherapy or immunotherapy (approved or investigational)
- TNF pathway inhibitors or PI3 kinase inhibitors
- Systemically active steroids for more than 3 days or use of any systemic steroids within 21 days before or after dosing, with the exception of study-prescribed steroids
- Any other investigational product
- Filgrastim (Neupogen® or granulocyte colony-stimulating factor) or Sargramostim (Leukine® or GM-CSF) should not be administered 14 days prior to or 14 days after any CRS-207 dose. Approval must be obtained from the Study Medical Monitor for a subject to continue dosing if administered within this timeframe.
- Prophylactic vaccines (e.g. pneumococcal vaccine, influenza vaccine) should not be administered 14 days prior to or 14 days after any CRS-207 dose. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed within specified timeframes. However, intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed. Approval must be obtained from the Study Medical Monitor for a subject to continue dosing if a prophylactic vaccine is administered within this timeframe.
- Live vaccines (examples of live vaccines include, but are not limited to: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, intranasal influenza vaccines (e.g. Flu-Mist®) and typhoid [oral] vaccine) and prohibited while on study treatment.
- Any UGT1A9 inhibitor, including acitretin, amitriptyline, androsterone, cyclosporine, dasatinib, diclofenac, diflunisal, efavirenz, erlotinib, estradiol (17-beta), flutamide, geftinib, gemfibrozil, glycyrrhetinic acid glycyrrhizin, imatinib, imipramine, ketoconazole, linoleic acid supplements, mefenamic acid, mycophenolic acid, niflumic acid, nilotinib, phenobartital, phenylbutazone, phenytoin, probenecid propofol, quinidine, ritonavir, sorafenib, sulfinpyrazone, valproic acid, and verapamil (note: propofol, when used for short-term sedation during surgical/biopsy procedures, is allowed after consultation with the Sponsor. The epacadostat dose may be taken on the morning of the procedure, and the evening dose held following the procedure. Epacadostat may be resumed the next day.)
- Use of the anticonvulsant carbamazepine (a UGT1A9 inducer) is discouraged. Because there is a potential interaction that could result in lower epacadostat exposures, an alternative to carbamazepine should be used, if possible.
- Use of any MAOI or drug associated with significant MAOI activity agents is prohibited from 21 days prior to Day 1 through 2 weeks after the final dose of epacadostat has been administered (see Appendix D).

- Any planned or emergency major surgery or surgical procedure; minor surgical procedures should be discussed with the Study Medical Monitor to determine if it is appropriate for the subject to continue study treatment. Placement of new implants or prosthetic devices will require subjects on CRS-207 to be discontinued from study treatment.

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

- General anesthesia or deep sedation
- Aspirin >325 mg/d (chronic daily use of aspirin ≤325 mg/d is allowed)
- More than 4 g/d of acetaminophen
- Systemic antibiotics
- Use of coumarin-based anticoagulants (e.g. Coumadin) is discouraged. Low-dose Coumadin (1 mg) is acceptable; however, doses that increase the INR are discouraged and will require dose modification. If an alternative to coumarin-based anticoagulants cannot be used, dose adjustment of the Coumadin may be needed. Based on the observed magnitude of epacadostat/warfarin PK interaction and PK/PD modeling results, for an epacadostat dose of 300 mg BID, the dose of warfarin should be reduced by approximately one-third after initiation of epacadostat administration based on approximately 30% to 40% reduction in S- and R-warfarin oral clearance values. Close INR monitoring is recommended for subjects on a stable dose of warfarin who are starting treatment with epacadostat. Based on PK/PD modeling, recommendations for warfarin dose modifications for subjects receiving other epacadostat doses, are summarized in Table 11 below based on the INR prior to starting epacadostat.

Table 11 Warfarin Dose Modifications

Stable Baseline INR	**Epacadostat Dose**		
	≤ 100 mg BID	**200 mg BID**	**300 mg BID**
INR ≤ 2.5	Close INR monitoring	Close INR monitoring	Reduce warfarin by ~33% and monitor INR
INR > 2.5	Close INR monitoring	Reduce warfarin by 20-25% and monitor INR	Reduce warfarin by ~ 33% and monitor INR

If subjects receive immunosuppressive medications on or after study, prophylactic antibiotics to prevent CRS-207 infection are strongly recommended for the duration of the treatment with the immunosuppressant (recommended oral 80 mg trimethoprim / 400 mg sulfamethoxazole once daily or 160 mg trimethoprim / 800 mg sulfamethoxazole (DS) three days a week).

5.6.3 Antibiotic Administration

Any subject who received CRS-207 will be administered a 7-day course of antibiotics at the EOT visit (once blood is drawn for cultures) and prior to receiving subsequent cancer-related (non-study) therapy. Site personnel will contact the subject to confirm compliance with antibiotic treatment.

Subjects with a central line port will receive 1 dose (2 g ampicillin or 3-5 mg/kg trimethoprim/sulfamethoxazole [in penicillin-allergic subjects]) of IV antibiotics through the port, followed by 6 days of oral antibiotics (the recommended course of oral amoxicillin (500 mg at 8-

hour intervals) or trimethoprim/sulfamethoxazole in penicillin-allergic subjects (160 mg trimethoprim/800 mg sulfamethoxazole at 12-hour intervals); all other subjects will receive a 7-day course of oral amoxicillin or trimethoprim/sulfamethoxazole (in penicillin-allergic subjects).

During or after study treatment, 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 Section 5.6.3.2 below).

Consult the package inserts for amoxicillin, trimethoprim, and sulfamethoxazole for product information on dosage and administration, contraindications, warnings/precautions, adverse reactions, and drug interactions.

5.6.3.1 Suspected Infection with CRS-207

[redacted]

5.6.3.2 Antibiotic Treatment for CRS-207 Infection

[redacted]

5.6.4 Documentation of Prior and Concomitant Medication and Therapy Use

All concomitant medications, therapies, and measures must be recorded in the eCRF, and any medication or therapy received or procedure performed within 28 days before study treatment begins and 30 days after the last dose of study drug, or until the subject completes the Safety Follow-up Visit, will be recorded in the eCRF. In addition, all prior and post-study treatment cancer-related therapies and procedures will be recorded in the eCRFs. The generic name, dosage, duration, and reason for the concomitant medication or therapy should be documented.

Any changes to concomitant medication or therapy will also be documented. The medication record will be maintained after signing the informed consent form (ICF) to document concomitant medications and therapies, including any changes to the dose or regimen. Concomitant medications include any prescription, over the counter medications, or natural/herbal preparations taken or administered during the study period. Concomitant treatments and/or procedures that are required to manage a subject's medical condition during the study will also be recorded in the eCRF.

6 STUDY ASSESSMENTS

All study assessments will be performed as indicated in the Schedule of Events. The order of procedures is suggested by the order of mention within the schedule. See below for description and instructions on each assessment. Further details of study procedures and assessments can be found in the study reference manual.

6.1 Screening Period

Before screening assessments are conducted, the subject must be given a thorough explanation of the purpose and evaluations of the study. Subsequently, the subject must sign and receive a copy of an ICF that was approved by the Institutional Review Board (IRB) or Ethics Committee and Institutional Biosafety Committee (IBC) and an authorization for use and disclosure of protected health information before any study-specific procedure is performed. The ICF must be obtained before performing any study-specific procedures. However, assessments done as part of standard of care prior to ICF may be used if they are within the required screening period. An original signed consent form will be retained in the subject's source documentation at the site, and a copy will be provided for the subject to take home.

The Screening Period will be up to 28 days. Screening is the interval between the signing of the ICF and the day the subject receives the first dose of treatment in the study (Cycle 1 Day 1). Potential subjects will be evaluated for entry into the study according to the stated inclusion and exclusion criteria. Subjects who are identified during this screening as not eligible for study enrollment do not need to complete all screening procedures. The reason for ineligible status will be documented.

Procedures conducted as part of the subject's routine clinical management (e.g. blood count, imaging study) and obtained before signing of informed consent may be used for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed in the required timeframe of the study (i.e. within 28 days of Cycle 1 Day 1). All information associated with eligibility requirements must be entered into the appropriate eCRF pages.

Tests with results that fail eligibility requirements may be repeated once during the screening period if the Investigator believes the results to be in error. Additionally, a subject who fails screening may repeat the screening process 1 time if the Investigator believes there has been a change in eligibility status (e.g. after recovery from an infection).

The screening biopsy will be obtained once all other eligibility requirements are confirmed. Treatment assignment (Phase 1) or randomization (Phase 2) will be the final step in the screening process, prior to administration of study drug(s).

6.2 Treatment Period

Treatment will commence on Cycle 1 Day 1. Subjects will be considered in the Treatment Period until completion of the EOT visit. Treatment may continue as long as the subject has not met any criteria for study withdrawal; pembrolizumab may be administered a maximum of 24 months. Subjects may continue on treatment with radiographic PD if subject is clinically stable and the Investigator believes the treatment is providing benefit.

6.3 End-of-Treatment Visit (EOT)

If a decision is made that the subject will permanently discontinue study drug, the EOT visit should be conducted as soon as possible after the last dose of study drug. If the EOT visit coincides with a regular study visit, the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT page in the eCRF.

If the EOT Visit is >21 days after the last administration of study drug, procedures from the EOT and Safety Follow-up visits may be collected as a single Safety Follow-up Visit.

6.4 Safety Follow-up Visit

For all subjects, a Safety Follow-up Visit will be scheduled 30 days (+5 days) after the last dose of study drug. If the subject begins another anticancer therapy before the Safety Follow-up Visit, every effort will be made to complete all of the Safety Follow-up Visit assessments prior to commencing the new therapy. If a CT scan was collected within 9 weeks (±7 days) of the Safety Follow-up Visit, then a CT scan at the Safety Follow-up Visit will not be mandatory. Once new anticancer therapy has been initiated, the subject will move into the survival follow-up period.

If there is an adverse event in need of monitoring beyond the Safety Follow-up Visit, the subject will be followed until resolution or confirmed stability of the adverse event. Adverse events and SAEs must be reported up until at least 30 days after the last dose of study drug, the date of the Safety Follow-up Visit, or until study drug-related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. If a new anticancer therapy has been initiated, the subject will move into the survival follow-up phase.

6.5 Disease Follow-up

Subjects who discontinue study treatment for a reason other than radiographically confirmed PD will move into the disease follow-up phase and should be assessed every 9 weeks (±7 days) by radiologic imaging and CA-125, to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anticancer therapy, documented PD, death, withdrawal of consent, or the end of the study, whichever occurs first. Information regarding post-study anticancer treatment will be collected if new treatment is initiated.

6.6 Survival Follow-up and CRS-207 Surveillance

Once a subject has radiographically confirmed PD and discontinues study treatment, the subject moves into the Survival Follow-up phase. Subjects will be followed every 12 weeks (±7 days) by telephone or optional clinic visit to assess for survival status and subsequent cancer-related therapies. Blood for culture will also be collected for CRS-207 surveillance at [redacted]. Survival follow-up will continue until death, withdrawal of consent, or the end of the study, whichever occurs first. At the conclusion of the study, all remaining subjects who have received at least 1 dose of study treatment will be offered enrollment in a long-term follow-up study and continue to be followed for survival.

6.7 Unscheduled Visit

Unscheduled study visits may occur at any time if medically warranted. Additional assessments or blood draws may be necessary if clinically indicated. Any assessments performed at those visits should be recorded in the eCRFs.

7 CONDUCT OF STUDY ASSESSMENTS AND PROCEDURES

7.1 Study Enrollment

For Phase 1, an enrollment form will be completed and sent to the Sponsor (or designee) for treatment assignment upon determining that the subject is eligible for study entry. This will occur prior to the Cycle 1 Day 1 visit.

For Phase 2 (including Safety Run-in), upon determining that the subject is eligible for study entry, sites will contact the Interactive Response Technology (IRT) to obtain study Arm assignment.

Further instructions for subject treatment assignment (Phase 1) and treatment randomization (Phase 2) are provided in the Study Reference and IRT Manuals.

7.2 Demographics and Medical History

Demographic data and a disease-targeted medical and medication history will be collected at screening by the Investigator or qualified designee and will include date of birth, race, ethnicity (where allowed by local regulations), medical and surgical history, and concurrent illnesses assessed using the NCI CTCAE v4.[64] Medical history should include all active conditions and any condition considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study (e.g. date of diagnosis, primary tumor histology, prior systemic therapies, surgeries, radiation therapy, and stage of cancer) will be recorded separately and not listed in medical history.

7.3 Distribution of Subject Dosing Diary and Reminder Cards

Subjects may be provided with reminder cards at each visit. The subject reminder card will indicate the date/time of the next visit, and will also remind the subject when they should not take their morning dose of study drug (if they are receiving epacadostat).

Subject daily dosing diaries will be provided to subjects taking epacadostat in order to track date and time of all doses taken between clinic visits. Subjects will be instructed to return any unused study drug at each visit. All returned study drug must be held in quarantine until the Sponsor or representative (Clinical Research Associate [CRA]) completes drug accountability. Dosing diaries will be reviewed against unused study drug and any discrepancies will be noted and reviewed with the subject (Section 5.5.3).

Subjects receiving epacadostat will also be given an SS information sheet prior to their first dose of epacadostat. The information sheet describes signs and symptoms of SS and also instructs subjects to seek immediate medical care if any of these symptoms are observed.

7.4 Blood Cultures for CRS-207 Surveillance

Blood samples from subject's peripheral vein will be obtained at EOT and at all visits indicated after EOT to monitor for presence of CRS-207. For subjects with a central line port, a blood sample will also be taken through the port at time points indicated for CRS-207 testing. Subjects with samples positive for the presence of CRS-207 will initiate IV antibiotics per Section 5.6.3.2 and be re-tested until negative cultures are confirmed.

7.5 Tumor Biopsy

Detailed instructions for fresh tissue collection, processing, and shipment, as well as details for processing and shipping the archived tumor tissue samples, are provided in the Laboratory Manual.

Biopsies are to be performed in accordance with standard techniques. Biopsies may be from an area of primary or metastatic disease. The area biopsied should be recorded. The same area should be biopsied for post-treatment biopsy.

Paired tumor biopsies (pre-dose and on Cycle 2 Day 15 [+7 days]) are mandatory during the study. Biopsies should not be collected within 1 day of CRS-207 or pembrolizumab administration. If additional biopsies or relevant samples (e.g. pleural fluid) are collected for routine care during the course of study, a sample should be retained if possible for Sponsor research evaluation.

The tissue sample should have proper size to enable IHC analysis. Fine needle aspiration will not be acceptable. If a subject provides a baseline biopsy and then subsequently a second biopsy at Cycle 2 Day 15 cannot be obtained due to safety or accessibility issues then the subject may remain on study treatment if they do not otherwise meet the criteria for withdrawal.

Tumor samples will be used to determine change in CD8/T_{reg} (FoxP3) ratio before and post-treatment. Tumor IDO1, PD-L1 and mesothelin protein expression, degree and type of immune cell infiltration by IHC or another related method will be performed. Other exploratory biomarkers, including analysis of RNA based transcriptional profiles and somatic mutations, may be performed to evaluate genomic associations with response or resistance. Depending on emerging data and the availability of sufficient sample, the immune response to treatment may also be evaluated by T cell receptor (TCR) repertoire analysis to determine the modulation of T cell response in the tumor microenvironment. Biopsy specimens to evaluate toxicities may also be collected to evaluate target-related expression.

7.6 Exploratory Laboratory Evaluations

7.6.1 Immune Monitoring, Pharmacokinetic, and Pharmacodynamic Assessments

Samples will be collected according to the Schedule of Events. All analyses will be conducted by the Sponsor or Sponsor's designee.

Serum and plasma will be collected from on all subjects at baseline and on-treatment to perform immune analyses, including quantifying analytes such as cytokines, chemokines, antibodies, relevant tumor markers, and other markers of immune function. Peripheral blood mononuclear cells (PBMCs) will be collected from all subjects prior to and during treatment to be analyzed for changes in immune cell subsets and functions, protein composition, and transcriptional changes. Assays characterizing the T cell functional responses to tumor antigens or CRS-207 may be conducted in PBMCs.

.

In order to explore whether a diverse T cell repertoire is predictive of and/or T cell repertoire changes occur in response to therapy, sequencing of their TCR genes may be performed on DNA isolated from peripheral blood and tumor to quantify antigen-specific T cell. A similar analysis may be conducted examining B-cell diversity. Genetic markers associated with response or resistance may also be measured using peripheral blood DNA, and peripheral blood DNA may be used as a germline control to compare with tumor cell DNA.

Plasma and whole blood samples for pharmacodynamic analysis will be analyzed for changes in protein analytes such as antibodies, relevant tumor markers and markers of immune function by enzyme-linked immunosorbent assay, or other relevant methods including peptide or protein arrays for antibody profiling. Plasma levels of Trp and Kyn will be evaluated by liquid chromatography with tandem mass spectrometry to monitor systemic activity in modulating the IDO1 enzyme.

The whole blood samples for pharmacodynamic analysis will be analyzed for changes in markers of immune cell populations, including, but not limited to, markers for immune cell subsets, B cells, NK cells, and T cells.

Additional pharmacodynamic analyses may be evaluated at the discretion of the sponsor using excess samples.

7.6.2 Unused Research Samples

Following the trial, any remaining samples not used for analysis per protocol parameters may be banked for additional investigations by the Sponsor or designee. The use of such samples will be in compliance with guidelines defined by the Guidance on Informed Consent for *In Vitro* Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable[65] and the European Medicines Agency (EMA) Reflection Paper on Pharmacogenomic Samples, Testing and Data Handling.[66].

8 EFFICACY ASSESSMENTS

8.1 Tumor Imaging and Assessment

8.1.1 Initial Tumor Imaging

Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days before the first dose of study treatment. **The same imaging technique should be used on a subject throughout the study.** Baseline scan must be a contrast CT or MRI, except in circumstances where there is a contrast allergy or with Study Medical Monitor approval. When the CT component of a positron emission tomography (PET)/CT uses higher energy and thinner slices, it may be acceptable (with Study Medical Monitor approval). A standard, full assessment for lesions should be conducted at baseline, including CT or MRI scans of chest, abdomen, and pelvis. The same modality (CT or MRI) should be used for follow-up assessments every 9 weeks, including radiological assessments of all sites of disease present at baseline. In addition to radiological monitoring, all other lesions observed at the screening visit should be followed.

For selection of target lesions, RECIST v1.1 should be followed. For example, RECIST discourages selection of target lesions inside the field of prior irradiation. Lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless it is the solitary site of measurable disease AND there has been demonstrated progression in the lesion. Also, if a subject has only 1 measurable lesion, this lesion should not be biopsied (Exception: in Phase 1 as long as the subject has evaluable disease, i.e. can be followed by CA-125, biopsying the only measurable disease is acceptable).

8.1.2 Tumor Imaging During the Study

Tumor imaging should be continued on study treatment and the same imaging technique should be used in a subject throughout the study. Imaging should be performed every 9 weeks (±7 days) from the first dose of study treatment or more frequently if clinically indicated. Imaging should not be delayed for delays in cycle starts or extension of combination treatment cycle intervals.

Imaging should continue to be performed until documented PD, the start of new anticancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first. PD should be confirmed at least 4 weeks after the first scan indicating PD in clinically stable subjects.

Table 12 Imaging and Treatment After First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD	Repeat imaging at ≥ 4 weeks to confirm PD	Should continue study treatment while awaiting confirmatory scan	Repeat imaging at ≥ 4 weeks to confirm PD if possible	Discontinue treatment
Repeat scan confirms PD	No additional imaging required	Discontinue treatment	No additional imaging required	N/A
Repeat scan shows SD*, PR*, or CR*	Continue regularly scheduled imaging assessments every 9 weeks	Continue study treatment	Continue regularly scheduled imaging assessments every 9 weeks	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion**
* SD, PR, CR is based on new baseline from first evidence of PD **If treatment is delayed contact the Medical Monitor to review treatment plans (Section 5.4.1)				

In determining whether or not the tumor burden has increased or decreased, site study team should consider all target lesions as well as non-target lesions.

Scenarios where PD is confirmed at repeat imaging:

- Tumor burden remains ≥ 20% and at least 5 mm absolute increase compared to prior scan
- Non-target disease resulting in initial PD is worse (qualitative)
- New lesion resulting in initial PD is worse (qualitative)
- Additional new lesion(s) since last evaluation

8.1.3 Tumor Response

RECIST v1.1 will be used by the local site to determine eligibility however treatment decisions will be based on modified RECIST v1.1 (mRECIST) criteria because immunotherapeutic agents may produce antitumor effects by potentiating endogenous cancer-specific immune responses which may take weeks to emerge. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST criteria may not provide a comprehensive response assessment of immunotherapeutic agents. Therefore, mRECIST will be used with the following adaptation:

If radiologic imaging shows initial PD, tumor assessment should be repeated ≥ 4 weeks later in order to confirm PD while continuing study treatment while awaiting radiologic confirmation of progression. If repeat imaging shows a stability or reduction in the tumor burden compared to the initial scan demonstrating PD, treatment may be continued /resumed. If repeat imaging confirms progressive PD, subjects will be discontinued from study therapy. In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions.

In subjects who have initial radiological evidence of PD, it is at the discretion of the treating physician whether to continue a subject on study treatment until repeat imaging is obtained a

minimum of 4 weeks later. This clinical judgment decision should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

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

When feasible, subjects should not be discontinued until progression is confirmed. Subjects who are deemed clinically unstable are not required to have repeat imaging for confirmation of PD.

In all other instances, treatment decisions will be made based on investigator review of the clinical and radiographic data.

Response will additionally be assessed using RECIST v1.1 and GCIG CA-125 criteria (see Appendix B and Appendix C, respectively). After confirmation of PD, survival data will be collected at least every 12 weeks (±7 days) after the Safety Follow-up Visit until death, withdrawal of consent, or the end of the study, whichever occurs first.

8.2 Tumor Biomarker CA-125

Tumor biomarker CA-125 will be monitored before, during, and after the treatment course as indicated in the Schedule of Events. Subjects who discontinue treatment for reasons other than PD should continue to have CA-125 assessed every 9 weeks (±7 days) until the start of a new anticancer therapy, documented PD, death, or the end of the study, whichever occurs first. Tumor biomarker CA-125 analysis will be performed by the site's local laboratory. Additional CA-125 time points collected per institutional standard should also be entered into the eCRF. Subjects considered CA-125 evaluable should have CA-125 repeated no earlier than 28 days if a CA-125 is reduced by 50% from baseline. See Appendix C for more details.

8.3 Pharmacokinetics, Pharmacodynamics, and Tumor Biomarker Analysis

Samples will be used to perform the following immunological and tumor biomarker analyses: Plasma epacadostat pharmacodynamics (kyn/trp ratio), plasma pharmacokinetics for epacadostat, number of tumor infiltrating lymphocytes, and CD8/T_{reg} (FoxP3) ratio.

Plasma pharmacodynamic and epacadostat pharmacokinetics parameters will be assessed at multiple time points.

9 SAFETY ASSESSMENTS

Safety will be assessed during each cycle and within 30 days following final dose of study drug. Safety parameters will include SAEs, TEAEs, ECOG performance status, vital sign measurements, standard clinical laboratory parameters (serum chemistry, hematology, and urinalysis), shedding of CRS-207 (urine, oral swab, and rectal swab), clearance of CRS-207 (blood), ECG parameters, and physical examination findings.

9.1 Adverse Events

All pre-existing medical conditions will be recorded on the medical history eCRF. Starting with the first administration of study drug, any new event or experience that was not present at screening, or worsening of an event present at screening, is considered to be an adverse event. Unchanged, chronic conditions are not adverse events and should not be recorded on the adverse event page of the eCRF.

An adverse event is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product.

PD is a study endpoint and consequently, should not be reported as an adverse event/SAE. However, when a subject dies from PD with no other immediate causes, “disease progression” should be reported as an SAE if within the safety reporting period as described in Section 9.3. All adverse events, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

Adverse events, which include clinical laboratory test variables, will be monitored and documented from the start of study treatment until 30 days after treatment is discontinued. Subjects should be instructed to report any adverse event that they experience to the Investigator or study staff. Beginning with Cycle 1 Day 1, Investigators should make an assessment for adverse events at each visit and record the event on the appropriate adverse event eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate adverse event on the eCRF. Additionally, the condition that led to a medical or surgical procedure (e.g. surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an adverse event, not the procedure.

Any medical condition already present at screening or present prior to treatment assignment (Phase 1) or randomization (Phase 2) should not be reported as an adverse event unless the medical condition or signs or symptoms present at baseline change in severity or seriousness at any time during the study. In this case, it should be reported as an adverse event.

Clinically significant abnormal laboratory or other examination (e.g. ECG) findings that are detected during the study or are present at treatment assignment (Phase 1) or randomization (Phase 2) and significantly worsen during the study should be reported as adverse events. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal

laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Any abnormal test that is determined to be an error does not require reporting as an adverse event.

9.1.1 Assessment of Adverse Events by the Investigator

The severity of all adverse events should be graded according to the NCI CTCAE v4. These criteria can be found at http://ctep.cancer.gov/reporting/ctc.html. Any adverse event that changes in grade during its course will be recorded in the eCRF at the highest level experienced by the subject. For those adverse events not listed in the NCI CTCAE, the following grading system should be used:

- Mild (NCI CTCAE Grade 1): Transient symptoms, awareness of sign/symptom, but easily tolerated and no interference with subject's daily activities.
- Moderate (NCI CTCAE Grade 2): Marked signs/symptoms that interfere with subject's usual activities, but still acceptable.
- Severe (NCI CTCAE Grade 3): Incapacitating signs/symptoms which cause considerable interference with the subject's daily activities, unacceptable.
- Life-threatening (NCI CTCAE Grade 4): Life threatening or disabling adverse event.
- Death (NCI CTCAE Grade 5): Death-related adverse event.

Causality Assessment:

For the purposes of Investigational New Drug reporting "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. The Investigator is obligated to estimate the relationship between the investigational products and the occurrence of each adverse event or SAE by using his or her best clinical judgment. Other causes, such as the underlying disease, concomitant therapy, other risk factors and the temporal relationship of the event to the investigational products will be considered and investigated. The Investigator will also consult the IB or product labeling information for marketed products in the determination of the assessment. The Investigator should consider all possible etiologies for the adverse event and render a causality assessment based on the most likely contributing factor to the adverse event.

There may be situations when an SAE has occurred and the Investigator has minimal information to include in the initial report. However, it is very important that the Investigator always assess causality for every event before the transmission of the SAE. The Investigator may change his or her opinion of the causality in light of follow-up information, amending the SAE report. The causality assessment (see below) is one of the criteria used to determine regulatory reporting requirements and should not be left blank.

- No (unrelated, not related, no relation) – The time course between the administration of study drug and the occurrence or worsening of the adverse event is not consistent with a causal relationship to study drug and another cause (concomitant drugs, therapies, intercurrent illnesses, underlying disease, etc.) is the most likely etiology.
- 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.) appears to be more likely.

9.1.2 Adverse Events of Special Interest

Adverse events of special interest (AESIs) must be recorded as such in the eCRF as an AESI. AESIs must be reported within 24 hours of knowledge of the occurrence including a detailed narrative of the AESI. AESIs will be collected from the time of first dose of study drug until 30 days following the last dose of study drug, or the subject initiates alternative antineoplastic therapy that is not permitted during this study, and must be reported regardless of causality. All AESIs that the Investigator considers related to study drug occurring after the 30-day follow-up period must be reported to the Sponsor (including ALL suspected infections with CRS-207 and/or *Listeria*).

For this study AESIs include:

- Suspected infection with CRS-207 and/or *Listeria*
- The development of Serotonin Syndrome
- The development of autoimmune diseases
- The development of any of the followings:
    - ≥ Grade 3 diarrhea
    - ≥ Grade 3 colitis
    - ≥ Grade 2 pneumonitis
    - ≥ Grade 3 hypo- or hyperthyroidism

9.1.2.1 Adverse Events of Special Interest Related to Serotonin Syndrome

As noted in Section 1.3.4, there is a theoretical chance that epacadostat could cause an increase in serotonin levels in the brain that might trigger SS when administered in combination with other serotonergic agents.[60] This syndrome has been most closely associated with use of MAOIs, Demerol®, linezolid, or methylene blue; all of these agents are prohibited during the study. SSRIs and SNRIs are permitted in the study. Procedures listed in Section 5.4.6 will be implemented if subjects exhibit the signs and symptoms of SS described in Table 10, including tremor; hyperreflexia; and spontaneous, ocular, or inducible clonus together with agitation, fever, diaphoresis, or muscle rigidity.

9.1.2.2 Adverse Events of Special Interest Related to Persistent Infection with CRS-207

Suspected infection with CRS-207 and/or *Listeria* should be reported irrespective of temporal relationship to study drug administration. This includes scheduled blood cultures during post-treatment surveillance monitoring that are positive for CRS-207 or if a subject presents with symptoms suspicious for a *Listeria*-like infection and/or has tested positive for *Listeria* at a local hospital/clinic. Any occurrence of suspected infection with CRS-207 and/or *Listeria*, regardless of when the last CRS-207 infusion was administered, should be reported to the Sponsor.

9.2 Serious Adverse Events

An adverse event or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening adverse event;
  - NOTE: An adverse event or adverse reaction is considered "life-threatening" if, in view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires hospitalization or prolongation of existing hospitalizations;
  - NOTE: Any hospital admission with at least one overnight stay will be considered an inpatient hospitalization. An emergency room visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as adverse events and assessed for seriousness. Admission to the hospital for social or situational reasons (i.e. no place to stay, live too far away to come for hospital visits) will not be considered inpatient hospitalizations.
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect; or
- An important medical event.
  - NOTE: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

9.3 Serious Adverse Event Reporting − Procedures for Investigators

Initial Reports

All SAEs occurring from the time of treatment assignment (Phase 1) or randomization (Phase 2) until 30 days following the last administration of study drug, or the subject initiates alternative antineoplastic therapy that is not permitted during this study, must be reported to Medpace Clinical Safety within 24 hours of the knowledge of the occurrence (this refers to any adverse event that meets any of the aforementioned serious criteria). All SAEs that the Investigator considers related to study drug occurring after the 30-day follow-up period must be reported to the Sponsor. The Principal Investigator must notify the IRB and IBC of the SAE in writing (electronic transmissions acceptable), in accordance with IRB and IBC requirements.

To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, Medpace Safety personnel will be notified electronically and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC, send an email to Medpace Safety at Medpace-safetynotification@medpace.com

or call the Medpace SAE hotline (phone number listed below), and fax the completed paper SAE form to Medpace (fax number listed below) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Safety Contact Information: Medpace Clinical Safety
Medpace SAE hotline – USA:
Telephone: +1-800-730-5779, ext. 2999 or +1-513-579-9911, ext. 2999
Facsimile: +1-866-336-5320 or +1-513-579-0444
e-mail: medpace-safetynotification@medpace.com

Follow-up Reports

The Investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the subject dies.

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

9.4 Pregnancy Reporting

If the subject becomes pregnant during the study or within 30 days of discontinuing study drug, the Investigator should report the pregnancy to Medpace Clinical Safety within 24 hours of being notified. Medpace Clinical Safety will then forward the Exposure *In Utero* form to the Investigator for completion.

A subject becoming pregnant while on study drug will immediately be withdrawn from the study and early termination study procedures will be performed.

The subject should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify Medpace Clinical Safety. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

9.5 Expedited Reporting

The Sponsor will report all relevant information about suspected unexpected serious adverse reactions that are fatal or life-threatening as soon as possible to the FDA and other applicable regulatory authorities as applicable, and in any case no later than 7 days after knowledge by the Sponsor of such a case, and that relevant follow-up information will subsequently be communicated within an additional 8 days.

All other suspected unexpected serious adverse reactions will be reported to the FDA and other applicable regulatory authorities as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor.

The Sponsor will also inform all Investigators as required.

9.6 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

For purposes of this study, 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 an SAE (see Section 9.3 for reporting details).

There has been no clinical experience with overdosage of CRS-207, epacadostat, or pembrolizumab. Treatment of overdosage should consist of general supportive measures.

9.7 Clinical Laboratory Evaluations

The Investigator may use clinical judgment when determining the clinical significance of laboratory parameter findings throughout the study. The Study Medical Monitor may, depending on study criteria, be consulted before enrollment about a potential subject with abnormal laboratory values that are not considered clinically significant. Additional tests may be performed or repeated as clinically indicated.

9.7.1 Chemistry and Hematology

A comprehensive serum chemistry and hematology panel will be performed as indicated in the Schedule of Events; required analytes for this panel are listed in Appendix A, Clinical Laboratory Analytes. The chemistry and hematology panel will be performed by the site's local laboratory. Fasting is not required unless clinically indicated.

9.7.2 Liver Function Tests

LFTs will be performed as indicated in the Schedule of Events; required analytes for this panel are listed in Appendix A, Clinical Laboratory Analytes. If LFTs are found to be abnormal, frequency of monitoring should be increased to once per week until LFTs have resolved to baseline or corticosteroid treatment has begun, at which time chemistry test monitoring will be performed according to institutional standards or approximately weekly, whichever is shorter. Liver function does not need to be monitored once per week indefinitely for persistent low-grade abnormalities. Appropriate liver function monitoring intervals should be discussed with the Study Medical Monitor. LFTs will be performed by the site's local laboratory.

9.7.2.1 Potential Drug-Induced Liver Injury (Hy's Law)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential drug-induced liver injury (DILI) event (also known as Hy's Law). All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 9.3 for reporting details).

Potential DILI is defined as meeting all of the following criteria:

- Aminotransferase (ALT or AST) elevation $\geq$3 × ULN
- Total bilirubin $\geq$2 × ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
- ALP < 2 ULN

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

9.7.3 Urinalysis

Urinalysis will be performed as indicated in the Schedule of Events; required analytes for this panel are listed in Appendix A, Clinical Laboratory Analytes. Urinalysis will be analyzed by the site's local laboratory.

9.7.4 Coagulation

A coagulation panel will be performed as indicated in the Schedule of Events; required analytes for this panel are listed in Appendix A, Clinical Laboratory Analytes. If a coumarin-based anticoagulant is given, INR should be monitored as described in the Schedule of Events. Coagulation panel will be analyzed by the site's local laboratory.

9.7.5 Endocrine and Thyroid Function Testing

Endocrine and thyroid function testing will be performed as indicated in the Schedule of Events; required analytes for this panel are listed in Appendix A, Clinical Laboratory Analytes. Endocrine function testing will not be collected for CRS-207 monotherapy dosed subjects. The endocrine and thyroid function testing will be performed by the site's local laboratory.

9.7.6 Pregnancy Testing

Pregnancy testing will be performed as indicated in the Schedule of Events. A serum pregnancy test is required for women of childbearing potential only and must be performed and confirmed negative prior to the first dose of study drug. Urine pregnancy tests for women of childbearing potential should be repeated and confirmed negative on Day 1 of each cycle and at the Safety Follow-up Visit. Serum testing may be conducted if urine pregnancy testing in unavailable. Serum and/or urine pregnancy test may be conducted up to 3 days before each dosing cycle where indicated. Pregnancy testing will be performed by the site's local laboratory.

If the serum pregnancy test is negative after a urine test was positive, the Investigator will assess the potential benefit/risk to the subject and determine whether it is in the subject's best interest to resume study drug and continue participation in the study.

9.7.7 Additional Laboratory Assessments

CD4 count, HLA-typing (low resolution), and a virology screen (Appendix A) will be performed once during the study as indicated in the Schedule of Events.

9.7.8 Shedding and Clearance of CRS-207

During Phase 1 and the Safety Run-in of Phase 2 at select US centers only, urine, rectal swab, oral swab, and whole blood will be collected from subjects pre-dose, and at 6 hours, 18 to 24 hours, and Day 7 post-CRS-207 infusion on Cycle 1 and Cycle 2. **The central line MAY NOT be used for obtaining blood samples**. Additional assessments will be performed if results are positive for CRS-207 at the Day 7 time point. Samples will be sent to the central laboratory. Additional details on sample collection, processing, and shipping are provided in the Laboratory Manual.

9.7.9 Blood Cultures for CRS-207 Surveillance

Blood samples will be obtained from subject's peripheral vein and from the central line port, if applicable, at the EOT visit [redacted]

9.8 Vital Signs, Weight, and Height

Vital signs, including seated BP, pulse rate, respiratory rate, and temperature, will be performed for all Treatment Arms as indicated in the Schedule of Events. Pulse oximetry will be measured if clinically indicated. Vital signs will additionally be monitored during infusion, per the CRS-207 infusion guidelines (Section 5.5.2.1).

Weight will be taken on Day 1 of each cycle. Height is required at screening only.

9.9 Physical Examinations

9.9.1 Comprehensive Physical Examination

Physical examinations must be performed by a medically qualified individual such as a licensed Physician, Physician's Assistant, or an advanced Registered Nurse Practitioner, as local law permits. The comprehensive physical examination will include the following organ or body system assessments: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver and spleen); extremities; lymph nodes; and a brief neurological examination. Before the first dose of study drug, clinically significant abnormal findings should be recorded as medical history. After the first dose of study treatment, new clinically significant abnormal findings should be recorded as adverse events.

9.9.2 Symptom-Directed Physical Examination

For visits that do not require a full physical examination per the Schedule of Events, the Investigator or medically qualified designee will perform a symptom-directed evaluation as clinically indicated. The targeted physical examination will include assessment(s) of the body systems or organs, as indicated by subject symptoms, adverse events, or other findings. New clinically significant abnormal findings should be recorded as adverse events.

9.10 ECOG Performance Status

The ECOG Scale of Performance Status is recognized as a standard tool to measure disease impact on daily living activities. The ECOG scale will be used by site personnel to determine eligibility and characterize a subject's level of functioning (self-care, daily activity, and basic physical ability) as indicated in the Schedule of Events.

9.11 Electrocardiograms

ECG assessments will be conducted as indicated in the Schedule of Events. All 12-lead ECGs will be performed in triplicate with the subject in a recumbent or semi-recumbent position after 5 minutes of rest. In order not to confound interpretation of the ECG, if anti-emetics or other prophylactic agents are given then these should be given after the pre-dose ECG rather than before.

Clinically significant abnormal findings after signing informed consent should be recorded as an adverse event. The 12-lead ECGs will be interpreted by the Investigator at the site and will be used for immediate subject management. The decision to include or exclude a subject or withdraw a subject from the study based on an ECG flagged as "Abnormal, Clinically Significant" is the responsibility of the Investigator, in consultation with the Study Medical Monitor, as appropriate.

10 STATISTICS

10.1 Analysis Populations

The Full Analysis Set (FAS) includes all subjects who received at least 1 dose of study drug. FAS analyses will be conducted on the basis of the randomized treatment. All efficacy analyses will be assessed using the FAS.

A Per-Protocol Set (PPS) will also be used to analyze efficacy endpoints and will be based on study drug exposure (compliance and/or time on study drug) and major protocol deviations. The criteria for inclusion in the PPS will be finalized and documented in the statistical analysis plan (SAP) prior to database lock.

The Safety Set (SAF) includes all randomized subjects who received at least 1 dose of study drug. The SAF will be conducted on the basis of the actual treatment received. All safety analyses will be assessed using the SAF.

10.2 Statistical Methods

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

Phase 1 and Phase 2 will be analyzed separately. Data will be summarized descriptively for Phase 1 by cohort and overall and Phase 2 by Arm and overall. Descriptive summaries for categorical variables will include counts and percentages. Descriptive summaries for continuous variables will include means, medians, standard deviations and minimum and maximum values. Descriptive summaries of time to event data will include median, 25th and 75th percentiles and standard error. Graphical summaries of the data may be presented. All data will be listed for all subjects.

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

10.2.1 Analysis of Efficacy

All efficacy analyses will be conducted on both the FAS and PPS.

10.2.1.1 Objective Response Rate

Objective response rate (ORR) is defined as the proportion of subjects with PR or CR according to mRECIST. Subjects who discontinue prior to post-baseline tumor assessments will be considered as non-responders.

The primary definition for objective disease response is based on mRECIST. Analyses will be performed separately using objective disease responses definitions based on the mRECIST, RECIST v1.1, and GCIG CA-125 criteria. Analysis repeated for RECIST v1.1 and GCIG CA-125 are considered supportive.

Progressive serial elevation of serum CA-125 will be used to determine CA-125 response. Guidelines for using CA-125 response have been developed. Refer to Appendix C for Gynecological Cancer Intergroup Definitions for Response and Progression Based on CA-125 Quick Reference. Subjects should have a pre-treatment CA-125 of at least twice the ULN in order

to be considered for CA-125 response. Subjects are not evaluable by CA-125 if they have received mouse antibodies or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days. In those subjects considered evaluable by CA-125, a CA-125 response would be obtained the moment the CA-125 is reduced by 50% and this should be confirmed with a consecutive CA-125 assessment not earlier than 28 days after the previous one, with however the date of the first 50% reduction to be the reference date for the CA-125 response.

For each cohort in Phase 1 and each Arm in Phase 2, objective disease responses will be summarized by response at each visit and best objective response. The number of subjects with disease control, defined as subjects with best objective response of CR, PR or SD, will also be summarized.

For expansion to the second stage in Phase 2, ORR and PFS will be assessed using mRECIST as the primary measure for assessment.

10.2.1.2 Progression-Free Survival

PFS is defined as the time from the date of first dose to PD or death due to any cause. Subjects who do not experience PD and do not die on or before the data cut-off date will be censored at the time of last tumor assessment or data cut-off date, whichever is earlier. Subjects who do not experience PD and start new systemic therapy will be censored at the time the new systemic therapy was begun or the data cut-off date, whichever is earlier. Subjects with no assessments of PD will be censored at the time of first dose. Subjects who are lost to follow up for assessment of PD will be censored at their last tumor assessment or data cut-off date whichever is earlier. Kaplan-Meier methodology will be used to estimate median PFS for each cohort in Phase 1 and in each Arm in Phase 2.

The primary definition of PD for PFS is based on mRECIST. Analyses will be performed separately using objective disease responses definitions based on the mRECIST, RECIST v1.1, and GCIG CA-125 criteria. Analysis repeated for RECIST v1.1 and GCIG CA-125 are considered supportive.

10.2.1.3 Overall Survival

Duration of survival is defined as the time from first dose until date of death due to any cause. Subjects without documentation of death at the time of analysis will be censored as of the date the subject was last known to be alive. Kaplan-Meier methodology will be used to estimate the survival probabilities and median survival time for each cohort in Phase 1 and in each Arm in Phase 2.

10.2.1.4 Immune Biomarker Parameters

Changes in immune response parameters will be summarized using descriptive statistics by each cohort in Phase 1 and each Arm in Phase 2.

Tumor samples will be analyzed by multiplexed IHC to enumerate CD8/T_{reg} (FoxP3) ratio, biomarker expression, immune checkpoint expression including IDO, PD-L1 and tumor infiltrating lymphocytes. Plasma Kyn-Trp ratio, circulating tumor biomarkers, circulating cytokines and chemokines, circulating immune cell subsets and their activation status, listeriolysin (LLO) and mesothelin-specific T cells, and humoral responses against LLO, mesothelin, and other tumor antigens will be assessed.

10.2.2 Analysis of Safety

Safety assessments will occur on all subjects who received any study medication. All safety analyses will be performed for each cohort and overall in Phase 1 and each Arm and overall in Phase 2.

Terminations/premature withdrawals, adverse events, DLTs, vital signs, and laboratory data will be tabulated.

Terminations and premature withdrawals will be summarized by frequency counts and percentages.

Adverse events will be coded to a standard set of terms using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA) dictionary and graded according to NCI CTCAE v4. Adverse events will be listed individually and incidence of adverse events summarized by system organ class and preferred terms within a system organ class. Analysis of toxicity will focus on SAEs and adverse events ≥ Grade 3 and attribution to assigned therapy. Administration-site reactions will be listed and tabulated separately from the adverse events.

Changes in vital signs, hematology and clinical chemistry parameters from baseline to the end of the study will be examined. Treatment-emergent changes from normal to abnormal values in key laboratory parameters will be identified. Laboratory data will be summarized for each time point that specimens are collected. Changes in NCI toxicity grading of laboratory data will be presented using shift tables and listings of clinically significant values.

10.2.3 Interim Analysis

Safety data will be reviewed on an ongoing basis by the SRC.

For Phase 2 of the study, after 13 treated subjects are enrolled in an Arm (Stage 1), an additional 14 treated subjects will be enrolled in the Arm (Stage 2) if 1 or more subjects respond (objective disease response of CR or PR) or if the median PFS is at least 4.8 months. Objective response rate and PFS are based on mRECIST. If neither of the criteria for response and PFS is met, the preliminary anti-tumor activity in the Arm will be rejected and no further subjects will be randomized to the Arm.

10.2.4 Sample Size Determination

During Phase 1, dose escalation will be based on traditional escalation guidelines (3+3) to determine the RP2D and evaluate safety data (including DLTs and adverse events) of each planned treatment.

Phase 2 will be an open-label, randomized study design conducted in 2 stages to achieve up to 27 treated subjects per Arm. After 13 subjects in an Arm are randomized at the confirmed dose following the Safety Run-in (stage 1), an additional 14 subjects will be enrolled in that Arm (stage 2) if 1 or more subjects respond or if the median PFS is at least 4.8 months. If the criteria for either ORR or PFS are not met, the preliminary anti-tumor activity in the Arm will be rejected and no further subjects will be randomized to the Arm. If the Arm goes on to stage 2, a total of 27 treated subjects will be studied in that Arm. The Arm will be considered successful if 4 or more subjects respond or the median PFS is at least 4.8 months. If the criteria for either ORR or PFS are not met, the Arm will be rejected. This design is applied to each Arm independently. There are no formal comparisons planned between Arms.

This is an exploratory study of each Arm where the sample size and ORR and PFS criteria for each stage are based on clinical judgement; each Arm is assumed to be evaluated separately. Type 1 error will not be controlled over both Arms. The ORR criteria and number of subjects for each stage within Arm are based on a Simon minimax 2-stage design (null hypothesis that ORR ≤ 0.05 versus the alternative that ORR≥ 0.20 with alpha = 0.05 and power = 0.80). The PFS criteria are based on the lower limit of the 95% CI determined based on meta-analysis in the 3rd relapse patient population where the median PFS is 5.6 months, (95% CI: 4.8 to 6.2 months).[67] The one-sided test for PFS (i.e. observing median PFS≥ 4.8 months) has a Type I error rate of 0.0744 when the null hypothesis is that the median PFS=3.6 months, PFS is exponentially distributed, accrual is uniform, and total study duration is 30 months for 27 subjects enrolled over 24 months. For a one-sided test of observing PFS≥ 4.8 months, there is approximately 77% power to detect a median PFS of 5.6 months and 50% power to detect a median PFS of 4.8 months.

Assuming a non-negative correlation between the one-sided tests for ORR and PFS, the overall Type I error for either test criteria being met is at most 0.1203. There is at least 70% power to meet at least one of the test criteria if ORR=0.25 and median PFS=4.8 and at least 79% power if ORR=0.25 and median PFS=5.6.

.

11 DATA MANAGEMENT AND RECORD KEEPING

11.1 Data Management

11.1.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed by the CRA during monitoring visits. The CRAs will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data will be appropriately tracked in an audit trail in the EDC system. For those who fail screening, only demographics and reason for screen failure will be documented on the eCRF. If a subject withdraws from the study, the reason must be noted on the eCRF. If a subject is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data has been accounted for and electronically signed by the Investigator.

11.1.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

11.1.3 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure user-name and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

11.1.4 Medical Information Coding

For medical information, the following thesauri will be used:

- Latest version of MedDRA for medical history and adverse events, and
- World Health Organization Drug Dictionary for prior and concomitant medications.

11.1.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator in order to be considered complete.

11.2 Record Keeping

Records of subjects, source documents, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Trial Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

12 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

12.1 Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

12.2 Institutional Review Board and Institutional Biosafety Committee

Participating sites will be responsible for reporting to their IRB and IBC. The IRB and IBC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of subjects. The study will only be conducted at sites where IRB and IBC approval has been obtained. The protocol, IB, ICF, advertisements (if applicable), written information given to the subjects, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB and IBC by the Investigator.

Federal regulations and International Conference on Harmonisation (ICH) require that approval be obtained from an IRB and IBC prior to participation of subjects in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for subject recruitment, and any other written information regarding this study to be provided to a subject or subject's legal guardian must be approved by the IRB and IBC.

No study drug will be released to the site for dosing until written IRB authorization has been received by the Sponsor.

12.3 Informed Consent

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the IRB and IBC prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

The Investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the subject has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each subject before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, their representatives, auditors, the IRB and/or regulatory agencies. A copy of the signed ICF will be given to the subject.

12.4 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, Declaration of Helsinki, ICH GCP, and applicable regulatory requirements, and that valid data are entered into the eCRFs.

To achieve this objective, the monitor's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well organized, and easily retrievable data. Before the enrollment of any subject in this study, the Sponsor or their designee will review with

the Investigator and site personnel the following documents: protocol, IB, eCRFs and procedures for their completion, informed consent process, study drug accountability, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data is entered by the site, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log.

12.5 Disclosure of Data

Data generated by this study must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB as appropriate. Subjects or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Subject medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

12.6 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating subjects (sufficient information to link records, eg, eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

12.7 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

12.8 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 CFR §54. In addition, Investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

13 STUDY ADMINISTRATIVE INFORMATION

13.1 Protocol Amendments

Any amendments to the study protocol will be communicated to the Investigators by Medpace or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB, unless immediate implementation of the change is necessary for subject safety. In this case, the situation must be documented and reported to the IRB within 5 working days.

13.2 Address List

13.2.1 Sponsor

Aduro Biotech, Inc.
740 Heinz Avenue
Berkeley, CA 94710-2224 USA
Telephone: +1 510-848-4400
Facsimile: +1 510-848-5614

13.2.2 Contract Research Organization

Medpace, Inc.
5375 Medpace Way
Cincinnati, OH 45227 USA
Telephone: +1 513-579-9911
Facsimile: +1 513-579-0444

13.2.3 Drug Safety

Medpace SAE hotline – USA:
Telephone: +1-800-730-5779, ext. 2999 or +1-513-579-9911, ext. 2999
Facsimile: +1-866-336-5320 or +1-513-579-0444
e-mail: medpace-safetynotification@medpace.com

13.2.4 Biological Specimens

Refer to the Laboratory Manual for shipment instructions and addresses.

14 REFERENCES

1. Buys SS, Partridge E, Black A, et al. Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial. JAMA 2011;305:2295-303.
2. Cancer Facts & Figures. 2015. at http://www.cancer.org/%20acs/groups/content/@editorial/documents/document/acspc-044552.pdf.)
3. SEER Stat Fact Sheets: Ovary cancer. 2015. at http://seer.cancer.gov/statfacts/html/ovary.html.)
4. Ovarian, fallopian tube, and primary peritoneal cancer screening (PDQ®). 2015. 2015, at http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0032596/.)
5. SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations) National Cancer Institute. 2012. at http://seer.cancer.gov/archive/csr/1975_2009_pops09/#contents.)
6. Pujade-Lauraine E, Hilpert F, Weber B, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. J Clin Oncol 2014;32:1302-8.
7. Pujade-Lauraine E, Alexandre J. Update of randomized trials in recurrent disease. Ann Oncol 2011;22 Suppl 8:viii61-viii4.
8. Edwards SJ, Barton S, Thurgar E, Trevor N. Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for advanced recurrent or refractory ovarian cancer: a systematic review and economic evaluation. Health Technol Assess 2015;19:1-480.
9. Naumann RW, Coleman RL. Management strategies for recurrent platinum-resistant ovarian cancer. Drugs 2011;71:1397-412.
10. Buda A, Floriani I, Rossi R, et al. Randomised controlled trial comparing single agent paclitaxel vs epidoxorubicin plus paclitaxel in patients with advanced ovarian cancer in early progression after platinum-based chemotherapy: an Italian Collaborative Study from the Mario Negri Institute, Milan, G.O.N.O. (Gruppo Oncologico Nord Ovest) group and I.O.R. (Istituto Oncologico Romagnolo) group. Br J Cancer 2004;90:2112-7.
11. Sehouli J, Stengel D, Oskay-Oezcelik G, et al. Nonplatinum topotecan combinations versus topotecan alone for recurrent ovarian cancer: results of a phase III study of the North-Eastern German Society of Gynecological Oncology Ovarian Cancer Study Group. J Clin Oncol 2008;26:3176-82.
12. Lortholary A, Largillier R, Weber B, et al. Weekly paclitaxel as a single agent or in combination with carboplatin or weekly topotecan in patients with resistant ovarian cancer: the CARTAXHY randomized phase II trial from Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens (GINECO). Ann Oncol 2012;23:346-52.
13. Berek JS, Bast RC, Jr. Epithelial Ovarian Cancer. 6th ed. Hamilton, ON: BC Decker; 2003.
14. Disis ML. Immune regulation of cancer. J Clin Oncol 2010;28:4531-8.
15. Boon T, van der Bruggen P. Human tumor antigens recognized by T lymphocytes. J Exp Med 1996;183:725-9.
16. Ercolini AM, Ladle BH, Manning EA, et al. Recruitment of latent pools of high-avidity CD8(+) T cells to the antitumor immune response. J Exp Med 2005;201:1591-602.
17. Galon J, Costes A, Sanchez-Cabo F, et al. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. Science 2006;313:1960-4.

18. Quezada SA, Peggs KS. Exploiting CTLA-4, PD-1 and PD-L1 to reactivate the host immune response against cancer. Br J Cancer 2013;108:1560-5.
19. Spranger S, Koblish HK, Horton B, Scherle PA, Newton R, Gajewski TF. Mechanism of tumor rejection with doublets of CTLA-4, PD-1/PD-L1, or IDO blockade involves restored IL-2 production and proliferation of CD8(+) T cells directly within the tumor microenvironment. J Immunother Cancer 2014;2:3.
20. Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. Nature 2011;480:480-9.
21. Chang K, Pastan I. Molecular cloning of mesothelin, a differentiation antigen present on mesothelium, mesotheliomas, and ovarian cancers. Proc Natl Acad Sci U S A 1996;93:136-40.
22. Scholler N, Fu N, Yang Y, et al. Soluble member(s) of the mesothelin/megakaryocyte potentiating factor family are detectable in sera from patients with ovarian carcinoma. Proc Natl Acad Sci U S A 1999;96:11531-6.
23. Le Page C, Ouellet V, Madore J, et al. Gene expression profiling of primary cultures of ovarian epithelial cells identifies novel molecular classifiers of ovarian cancer. Br J Cancer 2006;94:436-45.
24. Portnoy DA, Auerbuch V, Glomski IJ. The cell biology of Listeria monocytogenes infection: the intersection of bacterial pathogenesis and cell-mediated immunity. J Cell Biol 2002;158:409-14.
25. Shen H, Slifka MK, Matloubian M, Jensen ER, Ahmed R, Miller JF. Recombinant Listeria monocytogenes as a live vaccine vehicle for the induction of protective anti-viral cell-mediated immunity. Proc Natl Acad Sci U S A 1995;92:3987-91.
26. Slifka MK, Shen H, Matloubian M, Jensen ER, Miller JF, Ahmed R. Antiviral cytotoxic T-cell memory by vaccination with recombinant Listeria monocytogenes. J Virol 1996;70:2902-10.
27. Bahjat KS, Liu W, Lemmens EE, et al. Cytosolic entry controls CD8+-T-cell potency during bacterial infection. Infect Immun 2006;74:6387-97.
28. Brockstedt DG, Giedlin MA, Leong ML, et al. Listeria-based cancer vaccines that segregate immunogenicity from toxicity. Proc Natl Acad Sci U S A 2004;101:13832-7.
29. Le DT, Brockstedt DG, Nir-Paz R, et al. A live-attenuated Listeria vaccine (ANZ-100) and a live-attenuated Listeria vaccine expressing mesothelin (CRS-207) for advanced cancers: phase I studies of safety and immune induction. Clin Cancer Res 2012;18:858-68.
30. Mellor AL, Munn DH. Tryptophan catabolism and T-cell tolerance: immunosuppression by starvation? Immunol Today 1999;20:469-73.
31. Munn DH. Blocking IDO activity to enhance anti-tumor immunity. Front Biosci (Elite Ed) 2012;4:734-45.
32. Godin-Ethier J, Hanafi LA, Piccirillo CA, Lapointe R. Indoleamine 2,3-dioxygenase expression in human cancers: clinical and immunologic perspectives. Clin Cancer Res 2011;17:6985-91.
33. Mellor AL, Munn DH. IDO expression by dendritic cells: tolerance and tryptophan catabolism. Nat Rev Immunol 2004;4:762-74.
34. Munn DH, Mellor AL. Indoleamine 2,3-dioxygenase and tumor-induced tolerance. J Clin Invest 2007;117:1147-54.

35. Mellor AL, Baban B, Chandler P, et al. Cutting edge: induced indoleamine 2,3 dioxygenase expression in dendritic cell subsets suppresses T cell clonal expansion. J Immunol 2003;171:1652-5.
36. Frumento G, Rotondo R, Tonetti M, Damonte G, Benatti U, Ferrara GB. Tryptophan-derived catabolites are responsible for inhibition of T and natural killer cell proliferation induced by indoleamine 2,3-dioxygenase. J Exp Med 2002;196:459-68.
37. Fallarino F, Grohmann U, You S, et al. The combined effects of tryptophan starvation and tryptophan catabolites down-regulate T cell receptor zeta-chain and induce a regulatory phenotype in naive T cells. J Immunol 2006;176:6752-61.
38. Zou W. Regulatory T cells, tumour immunity and immunotherapy. Nat Rev Immunol 2006;6:295-307.
39. Munn DH, Zhou M, Attwood JT, et al. Prevention of allogeneic fetal rejection by tryptophan catabolism. Science 1998;281:1191-3.
40. Uyttenhove C, Pilotte L, Theate I, et al. Evidence for a tumoral immune resistance mechanism based on tryptophan degradation by indoleamine 2,3-dioxygenase. Nat Med 2003;9:1269-74.
41. Muller AJ, DuHadaway JB, Donover PS, Sutanto-Ward E, Prendergast GC. Inhibition of indoleamine 2,3-dioxygenase, an immunoregulatory target of the cancer suppression gene Bin1, potentiates cancer chemotherapy. Nat Med 2005;11:312-9.
42. Huang L, Baban B, Johnson BA, 3rd, Mellor AL. Dendritic cells, indoleamine 2,3 dioxygenase and acquired immune privilege. Int Rev Immunol 2010;29:133-55.
43. Weinlich G, Murr C, Richardsen L, Winkler C, Fuchs D. Decreased serum tryptophan concentration predicts poor prognosis in malignant melanoma patients. Dermatology 2007;214:8-14.
44. Munn DH, Sharma MD, Hou D, et al. Expression of indoleamine 2,3-dioxygenase by plasmacytoid dendritic cells in tumor-draining lymph nodes. J Clin Invest 2004;114:280-90.
45. Okamoto A, Nikaido T, Ochiai K, et al. Indoleamine 2,3-dioxygenase serves as a marker of poor prognosis in gene expression profiles of serous ovarian cancer cells. Clin Cancer Res 2005;11:6030-9.
46. Brandacher G, Perathoner A, Ladurner R, et al. Prognostic value of indoleamine 2,3-dioxygenase expression in colorectal cancer: effect on tumor-infiltrating T cells. Clin Cancer Res 2006;12:1144-51.
47. Ino K, Yoshida N, Kajiyama H, et al. Indoleamine 2,3-dioxygenase is a novel prognostic indicator for endometrial cancer. Br J Cancer 2006;95:1555-61.
48. Nakamura T, Shima T, Saeki A, et al. Expression of indoleamine 2, 3-dioxygenase and the recruitment of Foxp3-expressing regulatory T cells in the development and progression of uterine cervical cancer. Cancer Sci 2007;98:874-81.
49. Witkiewicz A, Williams TK, Cozzitorto J, et al. Expression of indoleamine 2,3-dioxygenase in metastatic pancreatic ductal adenocarcinoma recruits regulatory T cells to avoid immune detection. J Am Coll Surg 2008;206:849-54; discussion 54-6.
50. Hamid O, Chasalow SD, Tsuchihashi Z, Alaparthy S, Galbraith S, Berman D. Association of baseline and on-study tumor biopsy markers with clinical activity in patients (pts) with advanced melanoma treated with ipilimumab. J Clin Oncol 2009;27:abstr 9008.

51. De Felice F, Marchetti C, Palaia I, et al. Immunotherapy of Ovarian Cancer: The Role of Checkpoint Inhibitors. J Immunol Res 2015;2015:191832.
52. Badoual C, Hans S, Fridman WH, Brasnu D, Erdman S, Tartour E. Revisiting the prognostic value of regulatory T cells in patients with cancer. J Clin Oncol 2009;27:e5-6; author reply e7.
53. Le DT, Jaffee EM. Regulatory T-cell modulation using cyclophosphamide in vaccine approaches: a current perspective. Cancer Res 2012;72:3439-44.
54. Santoiemma PP, Powell DJ, Jr. Tumor infiltrating lymphocytes in ovarian cancer. Cancer Biol Ther 2015;16:807-20.
55. Gattinoni L, Ranganathan A, Surman DR, et al. CTLA-4 dysregulation of self/tumor-reactive CD8+ T-cell function is CD4+ T-cell dependent. Blood 2006;108:3818-23.
56. Pamer EG. Immune responses to Listeria monocytogenes. Nat Rev Immunol 2004;4:812-23.
57. Portnoy DA. Manipulation of innate immunity by bacterial pathogens. Curr Opin Immunol 2005;17:25-8.
58. Serbina NV, Kuziel W, Flavell R, Akira S, Rollins B, Pamer EG. Sequential MyD88-independent and -dependent activation of innate immune responses to intracellular bacterial infection. Immunity 2003;19:891-901.
59. Torres D, Barrier M, Bihl F, et al. Toll-like receptor 2 is required for optimal control of Listeria monocytogenes infection. Infect Immun 2004;72:2131-9.
60. Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med 2005;352:1112-20.
61. Gangadhar TC, Hamid O, Smith DC, et al. Epacadostat plus pembrolizumab in patients with advanced melanoma and select solid tumors: Updated phase 1 results from ECHO-202/KEYNOTE-037. ESMO; 2016 Oct 10. p. 379-400.
62. Opinion of CCBS for classifying Listeria monocytogenes strains with deletions in the genes *prfA*, *hly*, *actA*, and *plcB*. 1999. at http://www.bvl.bund.de/EN/06_Genetic_Engineering/genetic_engineering_node.html.)
63. Basch E, Prestrud AA, Hesketh PJ, et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2011;29:4189-98.
64. Common terminology criteria for adverse events (CTCAE) Version 4.0. National Institutes of Health, National Cancer Institute, 2010. (Accessed Apr 26, 2016, at http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.)
65. Food and Drug Administration. Guidance on informed consent for in vitro diagnostic device studies using leftover human specimens that are not individually identifiable. 2006.
66. EMA. Reflection paper on pharmacogenomic samples, testing and data handling. In: (CHMP) CfHMP, ed. London, UK2007.
67. Hanker LC, Loibl S, Burchardi N, et al. The impact of second to sixth line therapy on survival of relapsed ovarian cancer after primary taxane/platinum-based therapy. Ann Oncol 2012;23:2605-12.

APPENDIX A: CLINICAL LABORATORY ANALYTES

Serum Chemistry	Hematology	Other
Albumin Amylase Bicarbonate Blood urea nitrogen Calcium Chloride Creatinine Glucose Iron Lactate dehydrogenase Lipase Magnesium Phosphorus Potassium Sodium Total protein Uric acid CRP (standard sensitivity)	**Complete blood count, including:** Hemoglobin Hematocrit Platelet count Red blood cell count Reticulocyte count White blood cell count **Differential count, including:** Basophils Eosinophils Lymphocytes Monocytes Neutrophils (ANC) CD4 Count (Screening Only)	**Pregnancy test:** Female subjects of childbearing potential only require a serum test at screening. Pregnancy tests (urine or serum if required) should be repeated as required per schedule of events. **Coagulation:** PT aPTT INR D-dimer Fibrinogen **HLA-typing** Low resolution (Screening only) **Liver Function (LFT) Monitoring** Alkaline phosphatase ALT AST Total bilirubin Direct bilirubin (only if total bilirubin is elevated above ULN at screening)
Urinalysis	**Virology Screening**	**Endocrine/Thyroid Monitoring**
Color and appearance pH and specific gravity Bilirubin Glucose Ketones Leukocytes Nitrite Occult blood Protein Urobilinogen	Hepatitis B (HBsAg) Hepatitis antibody (HCV-RNA, Qualitative) HIV	Adrenocorticotropic hormone Serum cortisol (9 AM) Luteinizing hormone Prolactin Thyroid stimulating hormone (TSH) Free thyroxine (FT4) Total triiodothyronine (T3) or Free Triiodothyronine (FT3)

ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; ANC= absolute neutrophil count; AST = aspartate aminotransferase; INR = international normalized ratio; HBsAg = Hepatitis B surface antigen; HCV-RNA = Hepatitis C virus ribonucleic acid; HIV = human immunodeficiency virus; LFT = liver function test; PT = prothrombin time.

APPENDIX B: RESPONSE EVALUATION CRITERIA IN SOLID TUMORS VERSION 1.1 QUICK REFERENCE

Apply RECIST v1.1 criteria to tumor assessment and record on the eCRF.

RECIST v1.1 Criteria

	RECIST v1.1
Measurable tumor burden	A maximum of 5 target lesions in total (and up to 2 per organ) can be identified at baseline and measured through the course of therapy.
Minimum size of measurable lesions	≥10 mm in LD and 2 times the slice thickness for extranodal lesions; ≥15 mm in SAD for nodal lesions; ≥10 mm in LD for clinical lesions (must be measured electronic calipers); ≥20 mm in LD for chest X-ray (if clearly defined & surrounded by aerated lung); CT is preferable; and Ultrasound cannot be used to measure lesions.
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 nonmeasurable. The sum of the diameters (LD for extranodal target lesions, SAD for nodal lesions) is followed through the course of therapy.
Bone lesions	A lytic or mixed lytic-blastic bone lesion with a soft tissue component assessed on CT/MRI can be measurable if the minimum size criteria are met. Blastic bone lesions and bone lesions assessed on bone scan, PET, or plain films are non-measurable.
Cystic lesions	Lesions that meet the criteria for radiographically defined simple cysts are not malignant. Cystic lesions thought to be metastases can be measurable if they meet the minimum size criteria. Noncystic lesions are preferable.
Lesions with prior local treatment	Lesions in previously irradiated areas (or areas treated with local therapy) are not measurable unless the lesion has progressed since therapy. Conditions should be defined in study protocols.
Too small to measure	If a target lesion becomes too small to measure, a default value of 5 mm is assigned. If the lesion disappears, the measurement is recorded as 0 mm.
Lesions which split or coalesce	If extranodal target lesions fragment, the LDs of the fragmented portions are added to the sum. If target lesions coalesce and cannot be distinguished, the LD of the coalesced lesion is added to the sum.
Definition of CR	Complete response requires the disappearance of all extranodal lesions, the regression of all nodal lesions to <10 mm SAD, and the normalization of tumor marker level.
Definition of PD	Progressive disease is assessed if the sum of the diameters has increased by ≥20% and ≥5 mm from nadir (including baseline if it is the smallest sum). Patients with measurable disease: for "unequivocal progression" based on non-target disease, there must be an overall level of substantial worsening that merits discontinuation of therapy (if target disease is SD/PR). Patients without measurable disease: for "unequivocal progression" of non-target disease, the increase in overall tumor burden must be comparable to the increase required for PD of measurable disease.
Assessment of new lesions	New lesions should be unequivocal and not attributable to differences in scanning technique or findings which may not be tumor (ie, 'new' bone lesions may be healing or flare of preexisting lesions). If one is equivocal, repeat scans are needed to confirm. If confirmed, PD is assessed at the date of the initial scan. Lesions identified in anatomic locations not scanned at baseline are considered new. New lesions on ultrasound should be confirmed on CT/MRI.

CR = complete response; CT = computed tomography; FDG-PET = positron emission tomography with fluorodeoxyglucose; LD = longest diameter; MRI = magnetic resonance imaging; PD = progressive disease; PET = positron emission tomography; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SAD = short axis diameter; SD = stable disease.

	RECIST v1.1
FDG-PET	New lesions can be assessed using FDG-PET: (-) PET at baseline and (+) PET at follow-up is PD based on a new lesion. No PET at baseline and (+) PET at follow-up is PD if the new lesion is confirmed on CT. If a subsequent CT confirms the new lesion, the date of the PD is the date of the initial PET scan. No PET at baseline and (+) PET at follow-up corresponding to pre-existing lesion on CT that is not progressing; not PD.
Recurrence of lesions	For a patient with SD/PR, a lesion which disappears and then reappears will continue to be measured and added to the sum. Response will depend upon the status of the other lesions. For a patient with CR, reappearance of a lesion would be considered PD.
Overall response	One overall response table integrates target, non-target and new lesions and another table integrates non-target and new lesions for the assessment of subjects without measurable disease.
Confirmation of response	Confirmation of PR/CR is ONLY required for non-randomized trials where response is the primary endpoint. In these trials, subsequent confirmation of PR with 1 interim timepoint of SD is acceptable.

CR = complete response; CT = computed tomography; FDG-PET = positron emission tomography with fluorodeoxyglucose; LD = longest diameter; MRI = magnetic resonance imaging; PD = progressive disease; PET = positron emission tomography; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SAD = short axis diameter; SD = stable disease.

APPENDIX C: GYNECOLOGICAL CANCER INTERGROUP DEFINITIONS FOR RESPONSE AND PROGRESSION BASED ON CA-125 QUICK REFERENCE

Based on "Definitions for Response and Progression in Ovarian Cancer Clinical Trials Incorporating RECIST 1.1 and CA-125," a set of agreements by the Gynecological Cancer Intergroup (GCIG), the following definitions will be used in this study:

Definition of Response

"A CA-125 response is defined as at least a 50% reduction in CA-125 levels from a pretreatment sample. The response must be confirmed and maintained for at least 28 days. Patients can be evaluated according to CA-125 only if they have a pretreatment sample that is at least twice the upper limit of the reference range and within 2 weeks before starting the treatment.

"To calculate CA-125 responses accurately, the following rules apply:

- Intervening samples and the 28-day confirmatory sample must be less than or equal to (within an assay variability of 10%) the previous sample.
- Variations within the reference range of CA-125 levels will not interfere with the response definition.
- For each patient, the same assay method must be used, and the assay must be tested in a quality control scheme.
- Patients are not evaluable by CA-125 if they have received mouse antibodies (unless the assay used has been shown not to be influenced by human antimouse antibody) or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days (eg, paracentesis). If assessing therapy that includes 2 treatment modalities for relapse (eg, surgery and chemotherapy), any CA-125 response results from both treatment modalities. CA-125 cannot distinguish between the effects of the 2 treatments.

"The date when the CA-125 level is first reduced by 50% is the date of the CA-125 response. To calculate response, an intent-to-treat analysis should be used that includes all patients with an initial CA-125 level of at least twice the upper limit of the reference range as eligible and evaluable. In addition, as a separate analysis, those patients who have a CA-125 response and whose CA-125 level falls to within the reference range can be classified as CA-125 complete responders. In Tables 2 and 3 [*per Rustin et al*] where CA-125 is stated as normalised or normal, means within the reference range. Patients who have a fall of CA-125 to within the reference range but whose initial CA-125 was less than twice the upper limit of the reference range have not had a CA-125 response and cannot therefore be classified as a CA-125 complete responder.

Definition of Progression on Therapy and Recurrence After Therapy According to CA-125

"Progression is conventionally defined according to RECIST 1.1 but can also be based on serum CA-125 [*defined in Rustin et al*]. However, in assigning the date of progression, PD by objective change in tumor size should always take precedence over CA-125 should it occur first. If measurable disease is reducing in size during treatment but the CA-125 results suggest progression [*defined in Rustin et al*], the patient should continue to receive protocol treatment. If measurable disease is stable but CA-125 indicates confirmed progression over at least 4 weeks, some protocols

may advise changing protocol treatment, unless there is the possibility that the therapy could be slowing the rate of rise of CA-125. If patients are having routine CA125 measurements as part of follow-up, the date of progression is likely to be several months earlier than symptoms or signs of progression develop. Therefore, when categorizing patients according to time to progression, it is necessary to specify how the date of progression was defined (CA-125 alone, CA125 and symptoms, and RECIST). Protocols will need to specify that these data have to be collected."

Source: Rustin GJS, Vergote I, Eisenhauer E, et al. Definitions for Response and Progression in Ovarian Cancer Clinical Trials Incorporating RECIST 1.1 and CA 125 Agreed by the Gynecological Cancer Intergroup (GCIG). Int J Gynecol Cancer. 2011;21:419-423.

CA 125 definitions agreed by GCIG November 2005

The GCIG has agreed criteria for defining response and progression of ovarian carcinoma which use the serum marker CA 125, and the situations where these criteria should be used. It is recommended that the appropriate definitions described in detail below are cut and pasted into clinical trial protocols. The GCIG requests that data from all trial centers using these definitions is made available to trial centers associated with the GCIG so that continual validation and improvement can be accomplished.

CLINICAL SITUATIONS WHERE CA 125 CRITERIA FOR RESPONSE AND PROGRESSION AS DEFINED BELOW ARE RECOMMENDED BY THE GCIG

	USE RECOMMENDED BY GCIG	NOT STANDARD AND NEEDS FURTHER VALIDATION	NOT RECOMMENDED BY GCIG
FRONT LINE TRIALS	CA 125 PROGRESSION		CA 125 RESPONSE
MAINTENANCE OR CONSOLIDATION TRIALS		CA 125 RESPONSE AND PROGRESSION	
RELAPSE TRIALS	CA 125 RESPONSE	CA125 PROGRESSION	

The GCIG recommends that for trials of relapsed ovarian cancer the following definition for response according to CA 125 be used in addition to the standard RECIST response criteria.

EVALUATION OF RESPONSE ACCORDING TO CA 125

Definition of response. A response according to CA 125 has occurred if there is at least a 50% reduction in CA 125 levels from a pretreatment sample. The response must be confirmed and maintained for at least 28 days. Patients can be evaluated according to CA 125 only if they have a pretreatment sample that is at least twice the upper limit of normal and within 2 weeks prior to starting treatment.

To calculate CA 125 responses accurately, the following rules apply:

- intervening samples and the 28-day confirmatory sample must be less than or equal to (within an assay variability of 10%) the previous sample.
- variations within the normal range of CA 125 levels will not interfere with the response definition.
- For each patient, the same assay method must be used and the assay must be tested in a quality-control scheme.
- Patients are not evaluable by CA 125 if they have received mouse antibodies (unless the assay used has been shown not to be influenced by HAMA[4,5]) or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days. If assessing therapy that includes two treatment modalities for relapse (e.g., surgery and chemotherapy), any CA 125 response results from both treatments modalities. CA 125 cannot distinguish between the effects of the two treatments.

The date when the CA 125 level is first reduced by 50% is the date of the CA 125 response. To calculate response rates, an intent-to-treat analysis should be used that includes all patients with an initial CA 125 level of at least twice the upper limit of normal as eligible and evaluable. In addition, as a separate analysis, those patients who have both a CA 125 response and whose CA 125 level falls to within the normal range, can be classified as CA 125 complete responders. Patients who have a fall of CA 125 to within the normal range but whose initial CA 125 was less than twice the upper limit of normal, have not had a CA 125 response and cannot therefore be classified as a CA 125 complete responder.

Evaluation of response according to CA 125 in patients receiving maintenance or consolidation therapy.

Patients whose CA 125 is greater than twice the upper limit of normal when they start maintenance or consolidation therapy can be evaluated according to the GCIG CA 125 response definition. It should be noted that there is no data to validate response evaluation in this situation. To prevent the prior therapy interfering with the response assessment the following requirement is recommended. Two pre-treatment samples no more than 8 weeks apart are required if test treatment is given as part of maintenance or consolidation therapy. For the test treatment to be evaluable according to CA 125 there must be no more than a 10% fall in CA125 between the two pretreatment samples. The sample closest in time to the test therapy should be considered the pre-treatment sample.

Evaluation of response according to CA 125 in patients receiving first line therapy.

The CA 125 response definition was produced to evaluate relapse therapy. If assessing therapy that includes two treatment modalities (eg surgery and chemotherapy), any CA125 response is a result of both treatments, and it should be clearly stated that CA125 cannot distinguish between the effects of the two treatments. It should be remembered that for a patient to be classified as a complete responder according to RECIST, tumor marker levels such as CA 125 must be within the normal range.

EVALUATION OF BEST OVERALL RESPONSE IN PATIENTS WITHOUT INITIAL MEASURABLE DISEASE AND EVALUABLE BY CA 125

CA 125 may be used to evaluate response in patients without initial measurable disease, either because no measurable disease can be detected or because appropriate scans have not been performed.

CA 125	Non-Target Lesions#	New Lesions	**Overall serological Response**	**Best Response for this category also requires**
Response and Normalized	CR	No	**CR**	confirmed and maintained for at least 28 days.
Response	Non-PD	No	**PR**	
Normalized but not response	Non-CR/Non-PD	No	**SD**	
Non PR/non PD	Non-PD	No	**SD**	
PD	Any	Yes or No	**PD**	
Any	PD*	Yes or No	**PD**	
Any	Any	Yes	**PD**	

#Non-target lesions include ascites and peritoneal thickening, which are not measurable according to RECIST
*Unequivocal progression in non-target lesions may be accepted as disease progression

EVALUATION OF BEST OVERALL RESPONSE IN PATIENTS WITH INITIAL MEASURABLE DISEASE AND EVALUABLE BY CA 125

A report that combines both CA 125 and RECIST criteria, is likely to include patients that are measurable by one or both of the criteria, who may have events at different time points. In patients that are measurable by both criteria the date of response will be the date of the earlier of the two events. The following rules apply when determining the best overall response. If patients have PD according to RECIST within 28 days of CA 125 response they are classified as PD. If the PD according to RECIST is > 28 days before or after the CA 125 response they are classified as PR. Patients whose best response according to RECIST is SD but who have a CA 125 response are classified as CA 125 responders.

BEST OVERALL RESPONSE IN PATIENTS WITH INITIAL MEASURABLE DISEASE AND EVALUABLE BY CA 125, COMBINING BOTH CRITERIA

Target Lesion~	Non Target #	New Lesion	CA 125	Overall Best Response	
CR	CR	No	Normal	CR	**Best RECIST response for this category also requires it to be confirmed and maintained for at least 28 days**
CR	Non CR Non PD	No	Not PD	PR	
CR	CR	No	PR not normal	PR	
PR	Non PD	No	Not PD	PR	
NE	Non PD	No	PR	PR	
PD or New >28 days from CA 125 PR *			PR	PR	
SD	Non PD	No	PR	PR	
SD	Non PD	No	Not PR or PD	SD	
PD or New ≤ 28 days from CA 125 PR*			PR	PD	
PD	Any	Yes or No	Any	PD	
NE	PD	Yes or No	Any	PD	
NE	Any	Yes	Any	PD	
NE	Any	Yes or No	PD	PD	

see text above
~ target lesions include up to 10 measurable lesions as defined by RECIST
# non-target lesions include ascites and peritoneal thickening which are not measurable according to RECIST
* patients who have a CA 125 response that occurs more than 28 days from PD according to RECIST are considered a PR according to best response, but PD if the RECIST PD is within 28 days of CA 125 response

REPORTING OF RESPONSE ACCORDING TO BOTH RECIST AND CA 125 CRITERIA

Responses should be reported separately for each criteria as shown below:

Criteria:	RECIST	CA125		Best Overall [c]
		Only	All CA 125 Evaluable [b]	
CR (%)	4 (11.4%)[a]	4 (40.0%)[d]	8 (19.0%) [d]	8 (17.8%)
PR (%)	5 (14.3%)	4 (40.0%)	6 (14.3%)	9 (20.0%)
SD (%)	16 (45.7%)	2 (20.0%)	20 (47.6%)	18 (40.0%)
PD (%)	10 (28.6%)	0 (0.0%)	8 (19.0%)	10 (22.2%)
Unknown (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Evaluable	35 (100.0%)	10 (100.0%)	42 (100.0%)	45 (100.0%)
Non-Evaluable	10	3		-[e]

a. RECIST includes normalization of CA125 to achieve CR (see best overall response table).
b. Includes all patients who are evaluable by CA125, either alone, or in combination with other evidence of disease.
c. Includes all evaluable patients in the study, regardless of method for assessing response (see best overall response table).
d. Includes all patients who had both a CA 125 response and their CA 125 level falls to within the normal range.
e. This column only includes eligible patients, i.e. evaluable by at least one of the criteria, therefore cell blank.

Definition of Progression on first line therapy and Recurrence after first line therapy according to CA 125.

Progression is defined according to RECIST but can also be based upon serum CA 125 (defined below) but tumour measurements should take precedence over CA 125. If measurable disease is shrinking during treatment, but the CA 125 indicates progression (as defined below) the patient should continue to receive protocol treatment. If measurable disease shows stable disease but CA 125 indicates progression after a minimum of 3 courses of chemotherapy, protocol treatment should be changed. If the GCIG definition based on CA 125 is used to define progression after relapse therapy it should be noted that it has not been validated.

EVALUATION OF PROGRESSION ACCORDING TO CA 125

Progression or Recurrence based on serum CA 125 levels will be defined on the basis of a progressive serial elevation of serum CA 125, according to the following criteria:

A. Patients with elevated CA-125 pretreatment and normalisation of CA-125 must show evidence of CA-125 greater than, or equal to, two times the upper normal limit on two occasions at least one week apart **or**
B. Patients with elevated CA-125 pretreatment, which never normalises must show evidence of CA-125 greater than, or equal to, two times the nadir value on two occasions at least one week apart **or**
C. Patients with CA-125 in the normal range pretreatment must show evidence of CA-125 greater than, or equal to, two times the upper normal limit on two occasions at least one week apart.

Elevated values must be confirmed by two separate measurements obtained at least one week apart. CA 125 progression will be assigned the date of the first measurement that meets the criteria as noted. Patients are not evaluable by CA 125 if they have received mouse antibodies (unless the assay used has been shown not to be influenced by HAMA[4,5])or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days.

A patient may be declared to have progressive disease on the basis of either the objective RECIST criteria or the CA 125 criteria. The date of progression will be the date of the earlier of the two events if both are documented

Definition of progression after first-line therapy in ovarian cancer as proposed by the GCIG

GCIG subcategorized group	RECIST Measurable/non-measurable disease		CA 125
A	Compared to baseline (or lowest sum while on study if less than baseline), a 20% increase in sum of longest diameters (RECIST definition) or Any new lesions (measurable or non-measurable) Date PD: date of documentation of increase or new lesions	**A N D / O R**	CA 125 ≥ 2 x ULN documented on two occasions # Date of PD: first date of the CA 125 elevation to ≥ 2 x ULN
B	As for A		CA 125 ≥ 2 x nadir value on two occasions # Date of PD: first date of the CA 125 elevation to ≥ 2x nadir value
C	As for A		As for A

GCIG groups A, B & C defined above.

Repeat CA 125 any time, but normally not less than 1 week after the first elevated CA 125 level. CA 125 levels sampled after patients received mouse antibodies (unless the assay used has been shown not to be influenced by HAMA[4,5])or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days, should not be taken into account.

1. Therasse P, Arbuck SG, Eisenhauer EA et al. J Natl Cancer Inst 2000, 92:205-216, New guidelines to evaluate the response to treatment in solid tumors.

2. Rustin GJ, Quinn M, Thigpen T et al. J Natl Cancer Inst 2004, 96:487-488, Re: new guidelines to evaluate the response to treatment in solid tumors [ovarian cancer]. Gynecologic Cancer Intergroup.

3. Vergote I, Rustin GJ, Eisenhauer EA et al. J Natl Cancer Inst 2000, 92:1534-1535, Re: new guidelines to evaluate the response to treatment in solid tumors [ovarian cancer]. Gynecologic Cancer Intergroup.

4. Taylor PT, Haverstick D. J Natl Cancer Inst 2005, 97:151, Re: new guidelines to evaluate the response to treatment in solid tumors [ovarian cancer].

5. Rustin GJS. J Natl Cancer Inst 2005, 97:152, Re: new guidelines to evaluate the response to treatment in solid tumors [ovarian cancer].

APPENDIX D: PROHIBITED MONOAMINE OXIDASE INHIBITORS AND DRUGS ASSOCIATED WITH SIGNIFICANT MONOAMINE OXIDASE INHIBITORY ACTIVITY

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

APPENDIX E: INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For Subjects Participating in the Study:

The following methods that can achieve a failure rate of <1% per year when used consistently and correctly are considered as highly effective birth control methods.

Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[1]
    - Oral,
    - Intravaginal, and
    - Transdermal,
- Progestogen-only hormonal contraception associated with inhibition of ovulation,[1]
    - Oral,
    - Injectable, and
    - Implantable,[2]
- Intrauterine device (IUD), [2]
- Intrauterine hormone-releasing system (IUS),[2]
- Bilateral tubal occlusion,[2]
- Vasectomized partner,[2,3] and
- Sexual abstinence.[4]

4. Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.
5. Contraception methods that in the context of this guidance are considered to have low user dependency.
6. Vasectomized partner is a highly effective method provided of avoiding pregnancy that partner is the sole sexual partner of the woman of child bearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success.
7. In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Source: CTFG 2014.

APPENDIX F: SCHEDULE OF EVENTS (PHASE 1 ONLY)

Study Phase	Screening	Treatment Period										Follow-up Period		
		Cycle 1				Cycle 2				Cycle 3 and Beyond [1]				
	Screening	Week 1		Week 2	Week 3	Week 1		Week 2	Week 3	Week 1	Week 2	EOT [2]	Safety Follow-up[3]	Survival Follow-up
Study Day	-28 to -1	1	2	8	15	1	2	8	15	1	8	ASAP After Last Dose	30 Days After Last Dose	Every 12 Weeks
Visit Window (Days)	-	-	-	±1	±1	-	-	±1	±1	-	±1		+5	±7
Study Procedures														
Informed Consent	X													
Inclusion/Exclusion Criteria	X													
Assignment/Randomization to Treatment Arm [4]		X												
Medical History	X													
Vital Signs, Height, Weight [5]	X	X	X	X	X	X			X	X			X	
Physical Examination [6]	X	X				X				X			X	
ECOG Performance Status	X	X		X	X	X			X	X			X	
Electrocardiogram [7]	X	X			X [7]					X			X	
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	
Prior and Concomitant Medications and Therapies [8]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Survival and Additional Treatment Status [9]														X
Laboratory/Sample Collection														
Virology Screen [10]	X													
Urinalysis	X												X	
CD4 Count	X													
Pregnancy Test [11]	X	X				X				X			X	
Clinical Hematology, Serum Chemistry, Liver Function [12]	X	X	X	X	X	X	X	X		X	X		X	
Coagulation Panel [13]	X	X											X	
CA-125 Assessment [14]	X	X				X				X		X		
Serum/Plasma for Immune Monitoring [15]		X	X	X		X	X	X		X	X	X		
HLA-Typing [16]	X													

Study Phase	Screening	Treatment Period										Follow-up Period		
		Cycle 1				Cycle 2				Cycle 3 and Beyond [1]				
	Screening	Week 1		Week 2	Week 3	Week 1		Week 2	Week 3	Week 1	Week 2	EOT [2]	Safety Follow-up[3]	Survival Follow-up
Study Day	-28 to -1	1	2	8	15	1	2	8	15	1	8	ASAP After Last Dose	30 Days After Last Dose	Every 12 Weeks
Visit Window (Days)	-	-	-	±1	±1	-	-	±1	±1	-	±1		+5	±7
Endocrine Testing [17]	X	X								X				
PBMC [18]		X		X		X		X		X	X	X		
Serum for Epacadostat (PK) [19]						X	X							
Shedding and Clearance [20]		X	X	X		X	X	X						
Blood sample for CRS-207 testing[28]												X		X
Archived Tumor Specimen	X													
Plasma/Whole Blood for Pharmacodynamic Analysis [21]		X	X			X	X			X		X		
Tumor Biopsy [22]	X								X					
Tumor Evaluation [23]	X	Every 9 weeks (± 7 days)											X	X [9]
Blood for CRS-207 Surveillance [28]												X		X
Investigational Product Administration														
Administer CRS-207 [24]		X				X				X				
Epacadostat [25]		X [25]		← BID →										
Epacadostat Compliance & Accountability [26]		X	X	X	X	X	X	X	X	X	X	X		
Other Concomitant Medication														
Antibiotics [27]												X		

Footnotes

1. Treatment will continue for 6 cycles as long as there is potential for clinical benefit. After 6 cycles, treatment may continue if there is continued potential benefit and upon approval from the Study Medical Monitor. After Cycle 3 Day 8, visits between administrations of CRS-207 will be conducted based on Investigator's discretion. After Cycle 3 Day 1, initiation of a new cycle may be delayed up to 3 days due to subject scheduling. Epacadostat should continue uninterrupted during the treatment period.
2. An EOT Visit will occur as soon as determined that the subject will permanently discontinue study treatment, and at least 7 days after the last dose of CRS-207. If the EOT visit coincides with a regular study visit, the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT page in the eCRF. If the EOT Visit occurs >21 days after the last administration of study drug, procedures from the EOT and Safety Follow-up visits may be collected as a single Safety Follow-up Visit.
3. A Safety Follow-up Visit will be scheduled 30 days (+5 days) post last dose of study treatment. If the subject begins another anticancer therapy before the Safety Follow-up Visit, every effort will be made to complete all of the Safety Follow-up Visit assessments prior to commencing the new therapy. If there is an adverse event in need of

monitoring beyond the Safety Follow-up Visit, the subject will be followed until resolution or confirmed stability of the adverse event. If a CT scan was collected within 9 weeks (±7 days) of the Safety Follow-up Visit, then a CT scan at the Safety Follow-up Visit will not be mandatory.

4. For Phase 1, enrollment form will be completed and sent to Medpace for treatment assignment. As an added safety measure during Phase 1, Dose Cohort 1 will have a staggered enrollment of no more than 1 new subject treated per week during the dose escalation phase. Thereafter, a decision to further stagger combination enrollment will be made by the SRC and will be based on emergent safety data.
5. Vital sign measurements consist of seated BP, pulse, respiratory rate, and temperature. Pulse oximetry will be measured if clinically indicated. Weight will be taken on Day 1 of each cycle. Height is required at screening only.
6. Complete physical examinations will be conducted at screening and Safety Follow-up Visits; symptom-directed physical examinations will be conducted on Day 1 of all other cycles and at the EOT visit. Physical exams may be conducted up to 3 days before dosing with CRS-207.
7. 12-lead ECG assessments will be conducted on all subjects at screening, Cycle 1 (Day 1 and Day 15), and on Day 1 of every odd numbered cycle (Cycle 3, Cycle 5, etc.) while on treatment. Serial ECGs will be collected pre-dose and approximately 60 to 90 minutes after the first dose of epacadostat at Cycle 1 Day 2. For Subject receiving CRS-207 monotherapy, ECG will be collected pre-dose and approximately 60-90 minutes after their CRS-207 infusion has begun. In order not to confound interpretation of the ECG, if anti-emetics or other prophylactic agents are given then these should be given after the pre-dose ECG rather than before. ECGs will be performed with the subject in recumbent or semi-recumbent position after 5 minutes rest. Subsequent ECGs will be obtained as clinically indicated, and at the Safety Follow-up Visit.
8. All concomitant medications and cancer-related therapies and procedures will be recorded within 28 days before study treatment begins and 30 days after the last dose of study drug, or until the subject completes the Safety Follow-up Visit. In addition, all prior and post-study treatment anticancer therapy will be recorded in the eCRFs.
9. Once a subject has radiographic confirmed PD, discontinues study treatment or starts a new anticancer therapy, the subject moves into the Survival Follow-up phase. Subject will be contacted every 12 weeks (by phone/email is permissible if no recent (with 14 days) medical charting is available) to collect data on survival and any additional cancer-related therapies that may have been administered. Follow-up will continue until death, withdrawal of consent, or the end of the study, whichever occurs first.
10. Virology screen will include the following: HIV antibody, hepatitis B (HBsAg), and hepatitis C (HCV-RNA, Qualitative); additional virology may also be evaluated. Virology screen will be performed by the site's local laboratory.
11. Serum pregnancy test is required for women of childbearing potential only and must be performed and confirmed negative prior to the first dose of study treatment. Urine pregnancy test for women of childbearing potential should be repeated and confirmed negative on Day 1 of each cycle and at the Safety Follow-up Visit. Serum testing may be conducted if urine pregnancy testing in unavailable. Serum and/or urine pregnancy test may be conducted up to 3 days before dosing with CRS-207. Pregnancy testing will be performed by the site's local laboratory.
12. Refer to Appendix A for complete list of clinical hematology, chemistry and liver function analytes. Day 1 blood draws may be taken up to 3 days before dosing with CRS-207. Blood draws required on Day 2 after CRS-207 dosing for Cycle 1 and Cycle 2; additional timepoints may be obtained if clinically indicated. For subject in Arm 3 at Cycle 3, chemistry, hematology and liver function should be collected on Day 2 after their first infusion of CRS-207. **To avoid inadvertent contamination of a central line (eg, infusion ports, PICC lines), blood draws MUST NOT be collected from a central line for at least 4 days after infusion of CRS-207 has started.** If LFTs are found to be abnormal (>Grade 2), frequency of monitoring should be increased to once per week until LFTs have resolved to baseline at which time chemistry test monitoring will be performed according to institutional standards or approximately weekly, whichever is shorter. Liver function does not need to be monitored once per week indefinitely for persistent low-grade abnormalities. Appropriate liver function monitoring intervals should be discussed with the Study Medical Monitor. Hematology, chemistry and liver panel will be performed by the site's local laboratory.
13. Coagulation panel will include the following: D-dimer, fibrinogen, INR of PT, and aPTT; INR should be monitored weekly for the first 4 weeks after initiation of coumarin-based anticoagulants (see Section 5.6.2 for anticoagulant restrictions) and upon discontinuation of epacadostat. Coagulation testing will be performed by the site's local laboratory.
14. CA-125 will be assessed at screening as close to but no more than 14 days before the first study treatment, then on Day 1 of each cycle while on treatment (or every 3 weeks if subject dosing is delayed). Subjects who discontinue treatment for reasons other than PD should continue to have CA-125 assessed every 9 weeks until the start of a new anticancer therapy, documented PD, death, or the end of the study, whichever occurs first. Additional CA-125 timepoints collected per institutional standard should also be entered into the eCRF. Subjects considered CA-125 evaluable should have CA-125 repeated no earlier than 28 days if a CA-125 is reduced by 50% from baseline. See section Appendix C for more details.
15. Approximately 7.5 mL of whole blood for immune monitoring will be drawn as indicated. After Cycle 3, serum and plasma for immune response analysis will be collected at odd numbered Cycles (eg, Cycle 5, Cycle 7, etc.) Plasma will not be collected for Day 8 time points. Samples will be sent to the central laboratory.
16. The HLA-typing should include type A and B of class I antigens, low resolution. HLA will be performed by the site's local laboratory.

17. Endocrine testing will include: adrenocorticotropic hormone, serum cortisol (9 AM), luteinizing hormone prolactin, thyroid stimulating hormone, free thyroxine (T4), total triiodothyronine (T3). After Cycle 3, endocrine testing will be completed every 12 weeks (at Cycle 7, Cycle 11, etc.) Endocrine testing will not be collected for CRS-207 monotherapy dosed subjects.
18. Approximately 70 mL of whole blood to be processed as described in the Laboratory Manual. After Cycle 3, PBMCs will be collected on Day 1 for odd numbered Cycles only (eg, Cycle 5, Cycle 7, etc.).
19. Serum PK sample (3.5 mL) for epacadostat will be taken on Cycle 2 Day 1 at pre-dose, 2 (+/- 5 minutes), 4 (+/-10 minutes), and 6 (+/-15 minutes) hours after the morning dose of epacadostat. A pre-dose PK sample will be collected on Cycle 2 Day 2. Samples will be sent to the Central Laboratory. Epacadostat will be administered in clinic on Cycle 2 Day 1 and Day 2 in order to collect pre-dose blood sample for PK. PK samples will not be collected for those on CRS-207 monotherapy .
20. In Phase 1 US sites only: urine, rectal swab, oral swab, and whole blood will be collected from subjects treated with CRS-207 pre-dose, and at 6 hours, 18 to 24 hours, and Day 8 post-infusion on Cycle 1 and Cycle 2. **DO NOT use the central line for blood sample collection**. Additional assessments will be performed if results are positive for CRS-207 at the Day 8 time point. Samples will be sent to the central laboratory.
21. Plasma and whole blood (7 mL) for pharmacodynamic analysis will be collected only for those who receive epacadostat) at the following timepoints: Cycle 1 Day 1 and Cycle 2 Day 1 pre-dose, 2, and 6 hours post-dose; Cycle 1 Day 2 and Cycle 2 Day 2 prior to epacadostat dose; and Cycle 3 Day 1 and every odd numbered Cycle Day 1 thereafter) prior to epacadostat dose.
22. Paired tumor biopsies collected during the screening period (pre-dose) and on Cycle 2 Day 15 (+7 days). Paired biopsies are mandatory during Phase 1. Fine needle aspiration will not be acceptable. Samples will be sent to the Central Laboratory.
23. Tumor evaluations will be performed using CT with contrast of the abdomen and pelvis (or MRI in case of contrast dye allergy) within 28 days prior to treatment, and repeated every 9 weeks (±7 days) after initiation of study drug using the same assessment technique. Subjects who discontinue treatment for reasons other than PD should continue to have their disease assessed by CT every 9 weeks (±7 days) until the start of a new anticancer therapy, documented PD, death, withdrawal of consent, or the end of study, whichever occurs first. Data from any standard of care CT scans may also be collected for tumor evaluation.
24. CRS-207 will be administered on Day 1 of each cycle via IV infusion over approximately 1 hour. Before each CRS-207 infusion, subjects will be pre-medicated with acetaminophen and saline will be given immediately before and after infusion with CRS-207 (Section 5.5.2.1). Vital signs (BP, pulse, respiratory rate, temperature) will be obtained every 30 minutes (+/- 5 minutes) during CRS-207 infusion and every hour (+/- 5 minutes) during post-infusion follow-up. Subjects will be observed for at least 4 hours after each infusion. Subjects who are not stable enough to be released at 4 hours after infusion should continue to be monitored until stable. Presence of fever alone does not indicate subject is not clinically stable. Document the time subject becomes stable in the medical records. **To avoid inadvertent contamination of a central line (eg, infusion ports, PICC lines), DO NOT administer CRS-207 or saline through a central line during infusion or for 4 days following infusion. DO NOT flush the central line for any reason during and for 4 days after CRS-207 infusion.**
25. Enough epacadostat will be dispensed to last one cycle. Phase Arm 1: Epacadostat will be administered orally starting on Day 2 and BID thereafter. Tablets will be taken at the assigned dose in the morning and evening, approximately 12 hours apart. Epacadostat will be administered in clinic on Cycle 2 Day 1 and Day 2 in order to collect pre-dose blood sample for PK. Epacadostat dosing does not apply to CRS-207 monotherapy (Phase 1, Arm 2).
26. At each visit, provide a dosing diary and instructions on recording each dose of epacadostat. Collect unused epacadostat and review competed dosing diary with subject at following visit.
27. A 7-day course of antibiotics will be administered at the EOT visit after blood has been collected for CRS-207 culture to ensure clearance of CRS-207. Antibiotic regimen must be completed prior to initiation of any other cancer-related therapy. 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 (refer to Section 5.6.3). Site personal will contact the subject by to confirm compliance with the antibiotic treatment and document in source and CRFs.
28. At EOT, blood for culture will be collected prior to initiation of antibiotics (if applicable, blood must also be collected through the central line port) to assess CRS-207 clearance. After EOT, blood for culture will be collected for CRS-207 surveillance at [redacted]

aPTT = activated partial thromboplastin time; ASAP = as soon as possible; BID = twice daily; BP = blood pressure; CA-125 = cancer antigen 125; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EOT = End-of-Treatment; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; INR = international normalized ratio; IRT = Interactive Response Technology; IV = intravenous; LFT = liver function test; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cells; PD = disease progression; PICC = peripherally inserted central catheter; PK = pharmacokinetic; PT = prothrombin; SRC = Safety Review Committee.