CLINICAL STUDY PROTOCOL

A Phase 2, Open-label Evaluation of CRS-207 and Pembrolizumab in Adults with Recurrent or Metastatic Gastric, Gastroesophageal Junction, or Esophageal Adenocarcinomas

Protocol Number:	ADU-CL-14
Original Protocol:	20 December 2016
Amendment 1:	17 July 2017
Amendment 2:	22 August 2017
Investigational Products:	CRS-207 (live, attenuated, double-deleted *Listeria monocytogenes* encoding human mesothelin [*Lm* Δ*actA*/Δ*inlB* hMeso]) Pembrolizumab (MK-3475)
IND Number:	13,389
Sponsor:	Aduro Biotech, Inc. 740 Heinz Avenue Berkeley, CA 94710 USA Telephone: +1 510-848-4400

1 SYNOPSIS

TITLE: A Phase 2, Open-label Evaluation of CRS-207 and Pembrolizumab in Adults with Recurrent or Metastatic Gastric, Gastroesophageal Junction, or Esophageal Adenocarcinomas

PROTOCOL NUMBER: ADU-CL-14

INVESTIGATIONAL PRODUCTS:

CRS-207 (live, attenuated, double-deleted *Listeria monocytogenes* encoding human mesothelin [*Lm* Δ*actA*/Δ*inlB* hMeso])

Pembrolizumab (MK-3475)

PHASE: 2

SITES: Approximately 10 – 15 sites planned in the United States

INDICATION: Treatment of patients with recurrent or metastatic gastric, gastroesophageal junction (GEJ), or esophageal adenocarcinomas following prior systemic chemotherapy

OBJECTIVES:

The objectives of the study are to evaluate CRS-207/pembrolizumab when administered to subjects with recurrent or metastatic gastric, GEJ, or esophageal adenocarcinomas with respect to:

- Safety and tolerability
- Tumor response and survival
- Characterization of immune responses, biomarker expression, and molecular characteristics of the tumor microenvironment

STUDY DESIGN:

The study is an open-label, single-arm, multicenter clinical study in approximately 79 adults with recurrent or metastatic gastric, GEJ, or esophageal adenocarcinomas who have received one or two prior systemic chemotherapy treatment regimens for advanced disease. Of the approximately 79 evaluable subjects, the study will seek to enroll approximately 50 subjects with gastric/GEJ adenocarcinomas and approximately 29 subjects with esophageal adenocarcinoma to achieve adequate representation of each tumor type.

The study design consists of a 28-day Screening Period, Treatment and Evaluation Period (including a Safety Run-in), and a Follow-up Period. CRS-207 and pembrolizumab will be administered in 3-week cycles. For Cycle 1, pembrolizumab (200 mg) will be administered by intravenous infusion (IV) over 30 minutes on Day 1 and CRS-207 (starting dose 1×10^9 colony-forming units [CFU]) will be administered IV over 1 hour on Day 2. If the infusions are well tolerated, pembrolizumab and CRS-207 may be administered on the same day (Day 1) for subsequent cycles. After 4 cycles, pembrolizumab will continue to be administered on Day 1 at each treatment cycle (every 3 weeks; Q3W), and CRS-207 will be administered once every 6 weeks (i.e. every other treatment cycle; Q6W). Treatment cycles will continue for up to 24 months as long as there is adequate safety and potential for clinical benefit. If radiographic disease progression is observed, clinically stable

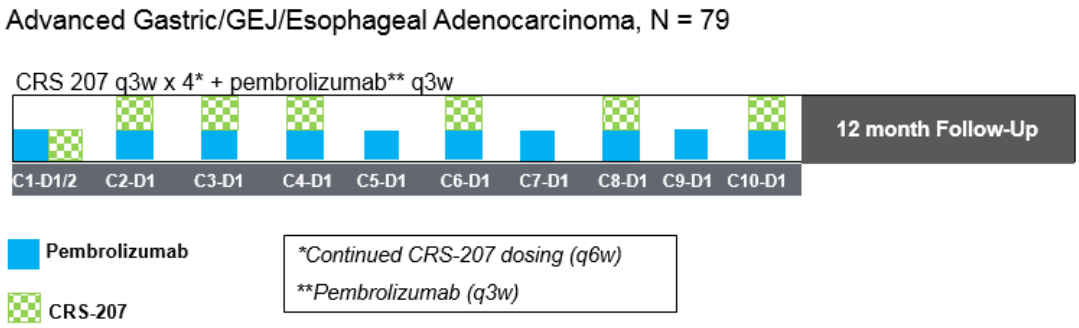
subjects who meet dosing eligibility may continue to receive CRS-207 and pembrolizumab according immune-related Response Criteria in Solid Tumors (irRECIST) guidelines in Section 11. Subjects who experience an unacceptable toxicity directly attributable to either pembrolizumab or CRS-207 may continue on study and receive either pembrolizumab or CRS-207 as single agent study treatment with approval by the Medical Monitor. Alternatively, study drug administration may revert back to consecutive day-dosing regimen as performed in Cycle 1 (Day 1 pembrolizumab and Day 2 CRS-207).

The Treatment and Evaluation Period is defined as the time from Day 1 until discontinuation of both CRS-207 and pembrolizumab, completion of an End-of-Treatment (EOT) Visit, and documented disease progression.

Blood will be collected at EOT to assess clearance of CRS-207 and at [redacted]. The EOT Visit will occur no more than 28 days after the last dose of study drug. If the subject has discontinued CRS-207 but continues on pembrolizumab, the subject will be asked to come back to the clinic for CRS-207 blood cultures [redacted]. If the subject begins another anticancer therapy before the end of the 28-day period, all EOT Visit assessments should be completed prior to commencing the new therapy. Unresolved adverse events (AEs) will be monitored until resolution or confirmed stability of the event. Subjects that discontinue all study drugs and complete the EOT without documented progressive disease (based on Response Evaluation Criteria in Solid Tumors [RECIST v1.1]) will be asked to complete Evaluation Visits for tumor imaging every 6 weeks until documented disease progression or start of another anticancer therapy. To eliminate any potentially residual CRS-207, subjects will be administered a 7-day course of antibiotics beginning at the EOT visit or 7 days after the last dose of CRS-207 (for patients continuing on pembrolizumab) and prior to receiving any subsequent cancer-related therapy.

At the end of the Treatment and Evaluation Period subjects will enter the Follow-up Period of the study and will be followed for survival and subsequent cancer-related therapies every 12 weeks until death or close of study by the Sponsor. The Sponsor may request survival status be assessed at additional time points during the course of the study. Sites will attempt to obtain vital status data 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. Follow-up will continue for at least 12 months from last dose of study drug.

ADU-CL-14 Study Schematic



A Safety Run-in will be completed since there are no precedent data on the use of pembrolizumab with CRS-207. Subjects will be monitored for unacceptable toxicity during the first 28 days (through 7 days after the Cycle 2 dose). During the Safety Run-in evaluable subjects are defined as those who remain on study for the 28-day monitoring period, subjects with unacceptable toxicity, and subjects who are discontinued for safety reasons at the Investigator's discretion (even if criteria for unacceptable criteria are not met). Treatment of the first 6 subjects that are followed for the 28-day period will be staggered with no more than 1 subject treated per week. In the event that 4 in up to 12 safety-evaluable subjects experience an unacceptable toxicity, the subsequent cohort of 12 subjects enrolled will be administered CRS-207 at a dose reduced by a half-log (dose level -1). In the event of 4 subjects in up to the next 12 safety-evaluable subjects enrolled experience an unacceptable toxicity, the subsequent cohort of 12 subjects enrolled will be administered a reduced dose of CRS-207 (dose level -2). For each dose reduction (to a minimum of 1×10^8 CFU) the first 12 subjects will be treated and unacceptable toxicities assessed as described above. No adjustments will be made to the pembrolizumab dose.

Safety data and all unacceptable toxicities will be reviewed by a Safety Review Team (SRT) comprised of participating investigators in the study, the Medical Monitor, and Sponsor representatives. Once the Safety Run-in is complete, safety will continue to be evaluated on an ongoing basis in this open-label study. Cumulative clinical experience with CRS-207 and pembrolizumab will be used to assess whether AEs are considered expected.

The Schedule of Events is provided in Table 1-1. Subjects who experience tolerability issues with same-day dosing may continue to follow the consecutive-day dosing regimen as in Cycle 1 with Day 1 pembrolizumab followed by Day 2 CRS-207 dosing (Table 1-2).

Tumor imaging and evaluation will be assessed at Screening and during the Treatment and Evaluation Period approximately every 6 weeks after initiation of study drug. Tumor measurement and assignment of response will be determined by local Investigators. For subjects on treatment more than 12 months, the frequency of imaging may be reduced to every 12 weeks. Peripheral blood will be collected to assess immune responses directed against *Listeria monocytogenes* (*Lm*), mesothelin, and other tumor-associated antigens. Archived tumor tissue and paired tumor biopsies (collected at Screening and during Cycle 2) 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.

INCLUSION AND EXCLUSION CRITERIA:

Inclusion Criteria

Individuals eligible to participate in this study must meet all of the following criteria:

1. Aged 18 years or older
2. Diagnosis with confirmed histology (pathology report required) of one or more of the following:
    - Histologically-confirmed gastric or GEJ adenocarcinoma (Siewert type II/III classification)
      [GEJ adenocarcinoma will be defined as primary tumor site within 5 cm proximal and distal of anatomic cardia]

Or

- Histologically-confirmed inoperable superior, medial, or distal third esophageal adenocarcinoma (Siewert type I classification may be included, provided there is no mixed histology)

3. Confirmed recurrent or metastatic disease
4. Received and experienced disease progression on, or following one or two prior chemotherapy regimens for advanced disease. Prior treatment must have included a platinum and a fluoropyrimidine.
5. HER-2/neu negative or, if HER-2/neu positive, disease must have previously progressed on treatment with trastuzumab
6. Measurable/assessable disease, as defined by RECIST v1.1. Target lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
8. Can provide the following tissue for PD-L1 and mesothelin biomarker analysis:
    - Archived primary tumor tissue (tissue from metastatic site acceptable if archived primary tissue is not available and primary site is not accessible for biopsy)
    - Pre-Treatment biopsy of either primary tumor or metastatic site
    - On-Treatment biopsy at Cycle 2, Day 15
9. Adequate organ and marrow function at Screening, as defined by:

Hematologic	**Renal**	**Hepatic**
WBC ≥ 3000/µL ANC ≥ 1500/µL ALC ≥ 800/µL Platelets ≥ 100,000/µL Hemoglobin ≥ 9 g/dL Albumin ≥ 3.0 g/dL INR or PT ≤ 1.5 × ULN [1] aPTT ≤ 1.5 × ULN [1]	Creatinine ≤ 1.5 × ULN; or measured /calculated creatinine clearance ≥ 60 mL/min if creatinine levels >1.5× ULN	AST/ALT ≤ 2.5 × ULN; or ≤5 × ULN for subjects with liver metastases Total bilirubin ≤ 1.5 × ULN; or ≤ 3 × ULN if due to Gilbert's disease; or direct bilirubin ≤ ULN if total bilirubin > 1.5 × ULN
ALC = absolute lymphocyte count; ALT = alanine aminotransferase; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; INR = international normalized ratio PT = prothrombin time; ULN = institutional upper limit of normal; WBC = white blood cell [1] If receiving anticoagulant therapy, values should be within therapeutic range of intended use		

Any Grade 3 or higher abnormality in any serum chemistry or hematology parameter should be discussed and approved by the Medical Monitor prior to enrollment (even if considered not clinically significant)

10. Women of childbearing potential (WOCBP) and fertile males with WOCBP partners must use highly effective contraception (CTFG, 2014) throughout the Treatment and Evaluation Period (from first dose and through 120 days after final dose of study drug). Contraception must include at least one barrier method to minimize risk of fluid transmission.

11. Provide written 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. Diagnosis of squamous or undifferentiated gastric cancer
2. Individuals with inaccessible tumors or for whom biopsy is contraindicated
3. Participated in any other study in which receipt of an investigational new drug or investigational device occurred within 28 days of first dose of study drug
4. Diagnosis of immunodeficiency, receiving TNF pathway inhibitors, PI3 kinase inhibitors, chronic systemic steroid therapy (> 10 mg/day of prednisone or equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug
5. Clinical evidence of ascites by physical exam
6. Prior anti-cancer monoclonal antibody within 4 weeks prior to first dose of study drug or has not recovered from adverse effects due to agents administered more than 4 weeks earlier
7. Prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to first dose of study drug, or has not recovered from adverse effects (i.e. ≤ Grade 1 or baseline) from adverse effects due to a previously-administered agent

   Note: Subjects with ≤ Grade 2 neuropathy or ≤ Grade 2 alopecia are an exception to this criterion.

8. Active second malignancy with the exception of any of the following:
   - Adequately treated basal cell carcinoma
   - Squamous cell carcinoma of the skin, or in situ cervical cancer
   - Low-risk prostate cancer (i.e. Gleason score < 7 and prostate specific antigen < 10 ng/mL); or
   - Any other cancer from which the individual has been disease-free for ≥ 3 years
9. 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.
10. Active infection requiring systemic therapy
11. Known **active** central nervous system metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging at least 4 weeks prior to the first dose of study drug and neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to first dose of study drug. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.
12. History of (non-infectious) pneumonitis that required steroids, or current pneumonitis
13. History of interstitial lung disease

14. Prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent, or agents targeting other checkpoint pathways (e.g. CTLA-4, LAG-3, GITR, OX40), or prior participation in Merck MK-3475 clinical trials
15. Prior immunotherapy with CRS-207 or any other *Listeria*-based agent, therapeutic cancer vaccine, adoptive T cell immunotherapy
16. Major surgery or significant traumatic injury occurring within 28 days prior to first dose of study drug

    Note: If major surgery occurred > 28 days prior to first dose of study drug, individual must have recovered adequately from the toxicity and/or complications from the intervention prior to first dose of study drug
17. Previous treatment with >2 systemic chemotherapy regimens for advanced disease
18. Known allergy to <u>both</u> penicillin and sulfa antibiotics
19. Unable or unwilling to withhold or discontinue any prohibited or restricted medications/procedures/immunizations for the specified windows during the study
20. If WOCBP, pregnant or breastfeeding; negative pregnancy status must be confirmed within 24 hours of first dose of study drug
21. Known valvular heart disease that requires antibiotic prophylaxis for prevention of endocarditis
22. Clinically significant heart disease (such as uncontrolled angina, myocardial infarction within 3 months of study initiation, congestive heart failure, or New York Heart Association Class III or IV heart failure)
23. History of autoimmune disease that has required systemic treatment in the past 2 years, including:
    - 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)

    Note: Individuals with vitiligo, Sjogren's syndrome, interstitial cystitis, Graves' or Hashimoto's Disease, celiac disease, diabetes mellitus type 1, or hypothyroidism stable on hormone replacement will be allowed with Medical Monitor approval.
24. Intercurrent illness that is either life-threatening or of clinical significance such that it might limit compliance with study requirements or in the Investigator's assessment would place the subject at an unacceptable risk for study participation;
25. Received a diagnosis of human immunodeficiency virus (HIV)
26. Received a diagnosis of hepatitis B, or hepatitis C for which there is no clear evidence of natural immunity, immunity subsequent to vaccination, or successful eradication of the virus following

antiviral therapy (individuals who are hepatitis C antibody positive may be enrolled if negative viral load confirmed at screening)

27. Subjects who have who have implanted medical devices that pose high risks for colonization and cannot be easily removed (e.g. artificial heart valves, pacemakers, prosthetic joints, orthopedic screw(s), metal plate(s)) if infection occurs. Other common devices such as venous access devices (e.g. Port-a-Cath or Mediport) may be permitted as well as arterial and venous stents and dental and breast implants that were placed more than 3 months prior to first dose of study drug.
28. Prior severe hypersensitivity (≥ Grade 3) to CRS-207, pembrolizumab, or any study drug excipients (e.g. yeast, glycerol)
29. Unhealed wound
30. History or evidence of inherited bleeding diathesis or coagulopathy
31. Received any prophylactic vaccine within 14 days of first dose of study drug or received a live vaccine within 30 days of planned start of study therapy. Seasonal flu vaccines that do not contain a live virus are permitted.

DURATION OF SUBJECT PARTICIPATION:

The Screening Period may last up to 4 weeks. The duration of 1 treatment cycle is 3 weeks. Subjects may continue to receive CRS-207/pembrolizumab for up to 24 months. After EOT or 7 days after last dose of CRS-207, [redacted]. Subjects will be observed for survival for at least 12 months from last dose of study drug. At the conclusion of the study, all remaining subjects in the Follow-up Period will be offered enrollment in a long-term observational study for survival.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

CRS-207 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 of CRS-207 is diluted in sterile saline and administered by IV infusion over approximately 1 hour.

Pembrolizumab for injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution. Each vial contains 100 mg/4 mL (25 mg/mL) solution in a single-use vial. Each 1 mL of solution contains 25 mg of pembrolizumab formulated in L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, USP. Pembrolizumab will be diluted in sterile saline administered at a dose of 200 mg via IV infusion over 30 minutes.

EFFICACY CRITERIA FOR EVALUATION:

Efficacy assessments will include a baseline tumor assessment by radiographic imaging to be performed within 28 days of starting study drug treatment, and repeat assessments approximately every 6 weeks after initiation of study drug using the same assessment technique (preferably by CT with contrast or magnetic resonance imaging (MRI) in case of contrast dye allergy). Tumor response will be assessed by investigators using RECIST v1.1 and irRECIST. Survival data will be

collected at least every 12 weeks after the EOT Visit for at least 12 months from the initiation of study drug.

Primary Efficacy Variable:

- Objective response rate (ORR), defined as the proportion of subjects with complete response (CR) or partial response (PR) as measured by RECIST v1.1

Secondary Efficacy Variables:

- Disease control rate (DCR), defined as the percentage of subjects with CR, PR, or stable disease (SD) per RECIST v1.1
- Progression-free survival (PFS) defined as time from first dose of study drug until disease progression or death
- Duration of response (DOR)
- Overall survival (OS), as measured from date of first dose of study drug until death

TUMOR TISSUE AND BIOMARKER ANALYSES:

PD-L1 and mesothelin expression along with additional markers of biological and immunological activity may be evaluated to explore the relationship to clinical response.

Archived primary tumor tissue will be collected for all enrolled subjects, when possible. Paired tumor biopsies of primary tumor or metastases (pre-treatment and on Cycle 2 Day 15) are required. If at Cycle 2 a subject's tumor is thought to be unsafe for biopsy by the Investigator, the site must discuss with the Medical Monitor.

Tumor tissue samples will be used to perform the following immunological and tumor biomarker analyses: PD-L1 status and mesothelin status; phenotyping and characterization of TILs and tumor microenvironment, functional genomic analyses, and T cell receptor (TCR) sequencing.

Baseline and longitudinal immune analysis of peripheral blood will be performed including immune cellular, molecular and genomic phenotyping and functional responses. Circulating proteins (cytokines, chemokines, tumor biomarkers and antibody responses) including mesothelin, carcinoembryonic antigen (CEA), vascular endothelial growth factor (VEGF), and cancer antigen 19-9 (CA19-9) will be assessed in serum and/or plasma.

Humoral and cellular immune responses directed against *Lm*, mesothelin, and other tumor-associated antigens may be evaluated by multiple approaches, including using enzyme-linked immunospot (ELISPOT), intracellular cytokine staining, and enzyme-linked immunosorbent assay (ELISA).

Additional exploratory immune and biomarker analyses on tumor tissue, peripheral blood mononuclear cells, serum, and plasma may be conducted.

SAFETY VARIABLES:

Safety parameters include serious adverse events (SAEs), treatment-emergent adverse events (TEAEs), infusion-related reactions, ECOG performance status, vital sign measurements, standard clinical laboratory parameters (serum chemistry, hematology, coagulation, thyroid function, and urinalysis), electrocardiogram (ECG) parameters, and blood cultures for CRS-207 clearance. AEs

will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE v4.03).

STATISTICAL ANALYSES

The descriptive summary for the categorical variables will include counts and percentages. The descriptive summary for the continuous variables will include means, medians, standard deviations, Q1, Q3, and minimum and maximum values. The descriptive summaries of time to event data will include median, 25th and 75th percentiles, and standard error. All data will be listed for all subjects.

This study is descriptive in nature; no formal hypothesis testing will be performed. All confidence intervals (CIs) will be 95%, unless stated otherwise.

The final analysis will be performed after all subjects have completed at least 6 cycles of treatment or discontinued study treatment and completed the EOT Visit. A supplemental analysis may be completed at the end of study that includes the cumulative data collected after the final analysis (i.e. through the Follow-up Period).

Safety Set (SAF) includes all subjects who received any study treatment (pembrolizumab or CRS-207). The SAF will be used for all analyses of safety data and may be used for select biomarker data.

Full Analysis Set (FAS) is defined as all subjects who received at least 1 dose of CRS-207. The FAS will be used for analysis of OS, immunogenicity and other biomarker data, and sensitivity analysis of select tumor-related endpoints.

Evaluable Analysis Set (EAS) is defined as all subjects who received at least 1 dose of CRS-207 and have at least one evaluable post-baseline RECIST tumor response assessment or were discontinued due to toxicity. The EAS will be the primary analysis set for the analyses of tumor-related endpoints (ORR, DCR, DOR, and PFS).

AE data will be coded to system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA; Version 18.1, or later). The number and percentage of subjects experiencing any TEAE, overall, and by system organ class and preferred term will be tabulated. The incidence rates adjusted by cumulative exposure will also be presented overall and by cycle. AEs associated with clinical laboratory parameters will be characterized according to NCI CTCAE, Version 4.03. Shifts in toxicity grades from baseline to each visit will be summarized.

Disease responses as determined by RECIST will be summarized by response level at each visit and best overall response. The ORR and DCR, along with a 95% CI will be summarized. PFS, DOR, and OS will be summarized using Kaplan-Meier methods.

SAMPLE SIZE DETERMINATION

This study is descriptive in nature, as such the sample size for this study is determined by practical rather than statistical considerations. Approximately 79 subjects will be enrolled with evaluable post-baseline tumor data. With 79 subjects, the precision for point estimate for ORR is as follows: the 95% CI width for ORR based on Wilson score intervals are at most the observed proportion +/- 0.108. If the observed ORR = 30.4% (24 of 79 subjects with PR or CR), the lower bound of the 95% CI would be 19.5%.

Table 1-1 Schedule of Events: Same-day (D1) Dosing Regimen

Study Phase	Screen	Cycle 1 [1]				Cycle 2 [1]				Cycle 3 [1]			Cycle 4 [1]		Cycle 5 and all future odd numbered cycles [1]	Cycle 6 and all future even numbered cycles [1]	EOT [2]	Follow-up
Study Day	**-28 to -1**	**1**	**2**	**3**	**7**	**1**	**2**	**7**	**15**	**1**	**2**	**7**	**1**	**7**	**1**	**1**	**±7**	[redacted]
Visit Window (days)	**-**	**-**	**-**	**-**	**±1**	**±3**	**±1**	**±1**	**-7**	**±3**	**±1**	**± 1**	**±3**	**±1**	**±3**	**±3**		
Study Procedures																		
Informed Consent	X																	
Inclusion/Exclusion Criteria	X	X																
Medical History, Height	X																	
Archived Tumor Specimen [3]	X																	
Tumor Biopsy [4]	X								X									
CT Tumor Evaluation [5]	X									X					X		X	
Survival, additional treatment [6]																		X
ECOG Performance Status	X	X				X				X			X		X	X	X	
Vital Signs, Pulse Oximetry [7,19, 20]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Examination and Weight [8]	X	X				X				X			X		X	X	X	
Adverse Events [9]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Electrocardiogram [10]	X	X	X			X				X			X		X	X	X	
Laboratory Sample Collection [11]																		
Virology Screen [12]	X																	
CD4 and CD8 Counts [13]		X																
Thyroid Function [14]		X								X					X		X	
Hematology, Chemistry [15]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Coagulation Panel [15, 16]	X	X	X			X				X			X			X	X	
Urinalysis	X	X				X				X			X				X	
Pregnancy Test [17]	X	X				X				X			X		X	X	X	
HLA-typing [13]		X																
Whole Blood for PBMC [18]		X			X	X		X	X	X		X	X	X		X	X	
Serum and Plasma for immune monitoring [18]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood for CRS-207 Surveillance [19]																	X	X
Study Medications																		
Pembrolizumab [20]		X				X				X			X		X	X		
CRS-207 [21]			X			X				X			X			X		
Antibiotics (with diary) [22]																	X	

Table 1-2 Schedule of Events: Consecutive-day (Day 1 and 2) Dosing Regimen (for Subjects with Tolerability Issues)

Study Phase	Screen	Cycle 1 [1]				Cycle 2 [1]					Cycle 3 [1]				Cycle 4 [1]			Cycle 5 and all future odd numbered cycles [1]	Cycle 6 and all future even numbered cycles [1]		EOT [2]	Follow-up
Study Day	**-28 to -1**	**1**	**2**	**3**	**7**	**1**	**2**	**3**	**7**	**15**	**1**	**2**	**3**	**7**	**1**	**2**	**7**	**1**	**1**	**2**	±7	[redacted]
Visit Window (days)	-	-	-	-	±1	±3	-	±1	±1	-7	±3	-	± 1	±1	±3	-	±1	±3	±3	-		
Study Procedures																						
Informed Consent	X																					
Inclusion/Exclusion Criteria	X	X																				
Medical History, Height	X																					
Archived Tumor Specimen [3]	X																					
Tumor Biopsy [4]	X									X												
CT Tumor Evaluation [5]	X										X							X			X	
Survival, additional treatment [6]																						X
ECOG Performance Status	X	X				X					X				X			X	X		X	
Vital Signs, Pulse Oximetry [7,19,20]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Examination and Weight [8]	X	X				X					X				X			X	X		X	
Adverse Events [9]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Electrocardiogram [10]	X	X	X			X	X				X	X			X	X		X	X	X	X	
Laboratory Sample Collection [11]																						
Virology Screen [12]	X																					
CD4 and CD8 Counts [13]		X																				
Thyroid Function [14]		X									X							X			X	
Hematology, Chemistry [15]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Coagulation Panel [15, 16]	X	X	X				X					X				X				X	X	
Urinalysis	X	X				X					X				X						X	
Pregnancy Test [17]	X	X				X					X				X			X	X		X	
HLA-typing [13]		X																				
Whole Blood for PBMC [18]		X			X	X			X	X	X			X	X		X		X		X	
Serum and Plasma for immune monitoring [18]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Blood for CRS-207 Surveillance [19]																					X	X
Study Medication																						
Pembrolizumab [20]		X				X					X				X			X	X			
CRS-207 [21]			X				X					X				X				X		
Antibiotics (with diary) [22]																					X	

FOOTNOTES FOR Table 1-1 AND Table 1-2

1. CRS-207 administered each cycle for 4 cycles (i.e. Cycles 1-4) and then every 6 weeks (i.e. every other cycle) beginning Cycle 5 and beyond. Treatment with pembrolizumab may continue up to 24 months. After Cycle 4, initiation of a new cycle may be delayed up to 3 days due to subject scheduling.
2. EOT Visit will occur within 28 days (±7 days) after the last dose of study drug or prior to commencing the new therapy. If an AE requires monitoring beyond the EOT Visit, follow until resolution or confirmed stability of the event. After the EOT Visit, [redacted]
3. Archived Tumor Specimen of primary tumor is required and obtained prior to enrollment. Tissue from metastatic site acceptable if archived primary tissue is not available and primary site is not accessible for biopsy.
4. Tumor Biopsies must be processed for analysis as described in Laboratory Manual. Cycle 2 Day 15 biopsy should not be collected until at least 7 days have passed since CRS-207 administration, but no later than Day 15 of cycle to allow sufficient recovery time prior to CRS-207 administration. Fine needle aspiration is not acceptable. If additional biopsies are obtained during study period for any reason, residual tissue should be retained for Sponsor analysis.
5. Tumor Evaluation using CT with contrast (or MRI in case of contrast dye allergy) of the chest, abdomen and pelvis within 28 days prior to first dose of study drug, and repeated using the same assessment technique. For subjects on treatment more than 12 months, imaging may be reduced to 12 week intervals. Subjects that discontinue all study drugs and complete the EOT without documented PD will be asked to complete Evaluation Visits for tumor evaluation every 6 weeks until documented PD or start of another anticancer therapy. Response assessment performed using RECIST v1.1 and irRECIST.
6. Survival Follow up: [redacted]. A telephone contact should also be scheduled at least 90 days post-treatment discontinuation to satisfy reporting requirements for SAEs and events of clinical interest.
7. Vital Signs and Pulse Oximetry: BP, pulse, respiratory rate, and temperature are collected at indicated visits without drug administration.
8. Physical Exam and Weight: Complete physical examinations conducted at screening and EOT; symptom-directed physical examinations conducted on Day 1 of all other cycles. Assessment may be done up to 72 hours prior to visit.
9. Follow-up contact for AEs and concomitant medications will be conducted 1 day after each CRS-207 infusion (and one day after pembrolizumab infusions Cycle 5 and beyond where CRS-207 is not administered). Contact must be documented in the study records.
10. Electrocardiogram: For visits where pembrolizumab and CRS-207 are administered consecutively (Day 1 and Day 2), routine 12-lead ECGs will be performed prior to each infusion, immediately after the infusion, and at 1-hour post infusion. For visits where pembrolizumab and CRS-207 are administered on the same day, routine 12-lead ECGs will be performed prior to pembrolizumab infusion, immediately after pembrolizumab infusion, immediately after CRS-207 infusion, and at 1-hour post CRS-207 infusion. If abnormal at 1-hour post-infusion, repeat until baseline achieved. Beginning at Cycle 6 frequency may be reduced to every 12 weeks unless clinically indicated.
11. BLOOD DRAWS **MUST NOT** BE COLLECTED FROM A CENTRAL LINE FOR AT LEAST 4 DAYS AFTER INFUSION OF CRS-207
12. Virology screen includes: HIV antibody, hepatitis B surface antigen, and hepatitis C antibody; additional virology may also be evaluated. Subjects who are hepatitis C antibody positive and confirmed negative viral load at screening will be allowed to enroll.
13. CD4 and CD8 Counts and HLA typing are performed by central laboratory. Collection is described in the Laboratory Manual. If HLA sample is rejected for analysis, an additional sample may be collected at a later time point
14. Thyroid panel should be collected during ODD NUMBERED cycles only (i.e. every 6 weeks). Blood draws may be taken up to 72 hours before each required dosing cycle. Unresolved abnormal labs considered drug related AEs should be followed until resolution. Panel not required at EOT if labs are within normal range during treatment.
15. Hematology, serum chemistry: Blood draws may be taken up to 72 hours before each dosing cycle where study drug is administered.

16. Coagulation Panel may be repeated at same frequency as hematology/serum chemistry if clinically indicated; beginning at Cycle 6 frequency may be reduced to every 12 weeks unless clinically indicated.
17. Pregnancy Test: Serum pregnancy test required at screening, and urine pregnancy tests are required before doses on Day 1 of each cycle and EOT for WOCBP.
18. Whole blood for PBMC and Serum and plasma for immune monitoring collected and processed per Laboratory Manual. Samples should be collected prior to study drug administration. Cycle 2 Day 15 collection should be taken on day of biopsy. Additional samples may be collected at Investigator's discretion.
19. Blood for CRS-207 Surveillance will be collected at EOT or 7 days after last CRS-207 dose to assess clearance of CRS-207. Obtain sample(s) prior to initiation of antibiotics (blood must additionally be collected from the central venous access device if applicable). After last dose of CRS-207, blood will continue to be collected at [redacted]. Collection and shipment are described in the Laboratory Manual.
20. Pembrolizumab will be administered via IV infusion for 30 minutes. Obtain vital signs (BP, pulse, respiratory rate, temperature) prior to, and immediately following each pembrolizumab infusion. Pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons. If subjects on same-day dosing schedule experience severe infusion-related reactions related to the pembrolizumab infusion, the CRS-207 infusion may be delayed to Day 2.
21. CRS-207 will be administered as indicated via IV infusion over approximately 1 hour. Obtain vital signs (BP, pulse, respiratory rate, temperature) every 30 minutes during infusion and every hour during post-infusion follow-up. Subjects should be observed at least 4 hours after the first infusion and every cycle where there is a change in dose or dosing regimen. For all subsequent infusions observe subjects for at least 2 hours post infusion. Subjects may be released once they are considered stable; fever alone does not preclude release.
22. [redacted]

ABBREVIATIONS FOR Table 1-1 AND Table 1-2

AE = adverse event; BP = blood pressure; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = End-of-Treatment; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; irRECIST = immune-related RECIST; IV = intravenous; *Lm* = *Listeria monocytogenes*; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cells; [redacted]; RECIST = response evaluation criteria for solid tumors; WOCBP = women of child-bearing potential.

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3 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
ALC	Absolute lymphocyte count
ANC	Absolute neutrophil count
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
CA19-9	Cancer antigen 19-9
CEA	Carcinoembryonic antigen
CFR	Code of Federal Regulations
CFU	Colony-forming units
CI	Confidence interval
CR	Complete response
CRA	Clinical research associate
CT	Computed tomography
CTCAE	Common Terminology Criteria For Adverse Events
DCR	Disease control rate
DOR	Duration of response
EAS	Evaluable analysis set
EBV	Epstein-Barr virus
EC	Ethics committee
ECG	Electrocardiogram
ECI	Event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
ELISA	Enzyme-linked immunosorbent assay
ELISPOT	enzyme-linked immunospot
EOT	End of Treatment
EU	European Union
FAS	Full analysis set
FDA	United States Food and Drug Administration
FT3	free triiodothyronine
FT4	free thyroxine
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GEJ	gastroesophageal junction
GM-CSF	Granulocyte-macrophage colony-stimulating factor

Abbreviation	Definition
GVAX pancreas	Irradiated, whole-cell, allogeneic tumor immunotherapy
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IHC	Immunohistochemistry
INR	International normalized ratio of prothrombin time
IRB	Institutional Review Board
irAE	Immune-related adverse event
irRECIST	immune-related RECIST
IV	Intravenous
LADD	Live, attenuated, double-deleted
Lm	*Listeria monocytogenes*
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major histocompatibility complex
mOS	Median overall survival
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NSCLC	non-small cell lung carcinoma
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
PD-1	programmed death receptor-1
PD-L1	programmed death receptor ligand 1
PFS	Progression-free survival
PR	Partial response
PT	Prothrombin time
[redacted]	[redacted]
Q3W	Once every 3 weeks
Q6W	Once every 6 weeks
RECIST	Response evaluation criteria in solid tumors
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SRT	Safety review team
T3	Triiodothyronine
TIL	Tumor infiltrating lymphocytes
TCR	T cell receptor

Abbreviation	Definition
TSH	thyroid stimulating hormone
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor
WBC	White blood cell

4 INTRODUCTION

In 2015, the National Cancer Institute estimated 16,980 new diagnoses of esophageal cancer and 24,590 new diagnoses of gastric cancer will occur in the United States (US). Together these cancers account for approximately 3% of all new cancer cases. Overall 5-year survival rates are approximately 20% for esophageal cancer and 30% for gastric cancer; approximately 50% of patients present with unresectable or locally advanced disease at the time of diagnosis (NIH, 2015).

Gastric cancer remains the fourth commonest diagnosed cancer and is the second leading cause of cancer-related death (Jemal, 2011). Patients with gastric cancer typically present with advanced disease. More than 50% of patients undergo surgical resection; however, the majority of them relapse locally or with distant metastases.

With new diagnoses in more than 480,000 patients annually, esophageal cancer is the eighth most common cancer worldwide (Siegel, 2015). It is a highly lethal disease, causing more than 400,000 deaths per year (Ferlay, 2010). The incidence of esophageal adenocarcinoma is rapidly rising, whereas that of squamous-cell carcinoma remains unchanged (Parkin, 2001). Despite adequate preoperative staging, 25% of patients treated with primary surgery have microscopically positive resection margins (R1) and the 5-year survival rate rarely exceeds 40% (Devesa, 1998).

Numerous advances have been made in the management and understanding of gastric and esophageal cancer, including improvements in diagnosis, histologic classification, and molecular biology. Despite these advances, patients with gastric and esophageal cancer have a poor prognosis and there is a clear unmet medical need for new treatment. New therapeutic strategies such as immunotherapy are under investigation.

Several lines of evidence suggest gastroesophageal cancers are good targets for immunotherapy (reviewed in Wang, 2016). An association between tumor infiltrating lymphocytes (TIL) and survival was first proposed over 100 years ago. Since then numerous studies have shown an increased density of TILs (including intratumoral B cells and NK cells) is associated with favorable clinical outcomes in gastric and esophageal cancer. In particular, the Epstein-Barr virus (EBV) and Microsatellite Instability (MSI) subtypes have been shown to have significant immune signatures including increased density of TILs. MSI cancers are also characterized by increased mutational load and presentation of neo-antigens. With the significant clinical benefits from immune checkpoint blockade drugs, novel opportunities are emerging for immunotherapy of gastric and esophageal cancers.

4.1 CRS-207 Immunotherapy

4.1.1 Listeria monocytogenes-Based Immunotherapy

Listeria monocytogenes (*Lm*) is an attractive platform for presentation of tumor-associated antigens and activation of immune response directed against cancer cells. *Lm* provides both a

potent stimulation of innate immunity and also induces an adaptive immune response through recruitment and activation of $CD4^+$ and $CD8^+$ T-cells specific for encoded heterologous antigens (Bahjat, 2006; Portnoy, 2002; Shen, 1995; Slifka, 1996). Repeat dosing with *Lm* is feasible; previously existing anti-*Lm* immunity did not affect generation of a T cell response to a *Lm*-expressed antigen, nor reduce resulting therapeutic efficacy in a mouse B16 melanoma model system (Starks, 2004).

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. To address this safety concern a live, attenuated, double-deleted *Lm* (LADD) based immunotherapy platform was developed (ANZ-100). ANZ-100 has deletions of 2 genes, *actA* and *inlB* (*Lm* Δ*actA*/Δ*inlB*). These genes encode the virulence-determinant proteins ActA and Internalin B, two proteins that facilitate cell-to-cell spread and invasion of nonphagocytic cells, in particular hepatocytes (Brockstedt, 2004). The deletions limit growth in the liver, a principal target organ of infection by wild-type *Lm*, by blocking direct hepatocyte infection via the InlB-hepatocyte growth factor receptor interaction and ActA-mediated cell-to-cell spread into hepatocytes from infected liver-resident Kupffer cells (Dramsi, 1995; Portnoy, 2002). Uptake of ANZ-100 by macrophages and other phagocytic cells in the liver and spleen is retained and results in a local inflammatory response as well as activation and recruitment of natural killer cells and T cells to the liver. In mice, ANZ-100 retains the immunostimulatory potency of wild-type *Lm* but with 1000-fold attenuation of virulence (Brockstedt, 2004). In a Phase 1 dose-escalation study, ANZ-100 doses up to 3×10^8 colony-forming units (CFU) administered by intravenous (IV) infusion in adults with carcinoma and liver metastases were well-tolerated (Le, 2012).

4.1.2 CRS-207

Mesothelin is a tumor-associated antigen with limited expression on the surface of normal tissues, but highly expressed in many human tumors including virtually all mesothelioma (Hassan, 2004). Mesothelin is expressed in 44-50% of human gastric cancer; presence of luminal or membranous staining of mesothelin has been correlated with poor patient outcome (Einama, 2012; Illei, 2016). In esophageal adenocarcinoma, 29-46% of tumors stained positive for mesothelin; expression correlated with development of malignancy in cases of Barrett's esophagus (Alvarez, 2008; Rizk, 2012). These features make mesothelin an attractive target for active tumor-specific immunotherapy.

ANZ-100 was subsequently engineered to express mesothelin, resulting in CRS-207 (*Lm* Δ*actA*/Δ*inlB*/hMeso). CRS-207 contains an expression cassette encoding human mesothelin integrated at the *inlB* locus. After uptake of CRS-207 by dendritic cells and macrophages, mesothelin is expressed and released into the cytosolic compartment and subsequently processed through the endogenous major histocompatibility complex (MHC) Class I presentation pathway, resulting in activation of mesothelin-specific cell-mediated immunity (Le, 2012). Other mechanisms to activate mesothelin-specific, cell-mediated immunity may include uptake and

cross-presentation of antigens by dendritic cells and other cells after infection by CRS-207 and apoptosis. CRS-207 is a LADD construct rendering it greater than 1000-times less toxic in mice than wild-type *Lm* (Brockstedt, 2004). Nonclinical and clinical data are available and support continued clinical development.

4.1.3 Summary of Nonclinical Studies with CRS-207

A series of nonclinical studies in rodents (mice) and non-human primates (cynomolgus macaques) evaluated the pharmacology, pharmacokinetics (PK) and toxicology of CRS-207. In these studies, CRS 207 elicited mesothelin-specific cellular immunity and therapeutic efficacy in tumor-bearing mice. Repeated-dose safety studies in cynomolgus macaques with CRS-207 and the parent strain, ANZ-100, resulted in an equivalent pro-inflammatory response characterized by transient fluctuations in selected hematological and clinical chemistry parameters and reversible histopathology. Findings of the repeated-dose studies were consistent with a systemic proinflammatory response to a bacterial infection. At the highest dose, CRS-207 was detected in the blood 24 hours after administration, but was undetectable at 72 hours. There were transient and dose dependent decreases in red blood cell, platelet and white blood cell (WBC) counts. Hepatic and renal function changes were transient and generally less than two-fold from baseline. There were no discernible additive effects of repeat dosing. [redacted]

Overall, nonclinical studies support use of CRS-207 in humans at the proposed dose. A complete summary of nonclinical information on CRS-207 is provided in the Investigator's Brochure (IB).

4.1.4 Summary of Clinical Studies with 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. Information related to this study is briefly summarized below; 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 non-small cell lung carcinoma (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.

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 hypotension; 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.

4.2 Pembrolizumab in Gastric, Gastroesophageal Junction, and Esophageal Adenocarcinomas

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD 1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD 1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda™ (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the Investigator brochure.

Pembrolizumab has demonstrated initial clinical efficacy in single arm monotherapy trials in subjects with NSCLC, head and neck squamous cell carcinoma, urothelial cancer, gastric cancer, triple negative breast cancer and Hodgkin's Lymphoma as determined by response rate. Ongoing clinical trials are being conducted in these tumor types as well as a number of other advanced solid tumor indications and hematologic malignancies. For study details please refer to the pembrolizumab IB.

KEYNOTE-012 (NCT01848834) enrolled patients with recurrent or metastatic adenocarcinoma of the stomach or gastroesophageal junction (GEJ). Subjects were treated with pembrolizumab 10 mg/kg every 2 weeks for up to 24 months or until CR, disease progression, or unacceptable toxicity. Of 162 patients screened 65 (40%) were PD-L1 positive, of which 39 enrolled; 67% received ≥2 prior therapies. Median follow-up duration was 8.8 months. Objective response rate (ORR) was 22% (95% CI 10-39) by central review and 33% (95% CI 19-50) by investigator review. Median time to response was 8 weeks (range 7-16), with median response duration of 24 weeks (range 8+ to 33+ weeks). PD-L1 expression level was associated with ORR (1-sided P = 0.10). The 6-month progression-free survival (PFS) rate was 24%. Four subjects experienced 5 total Grade 3-5 drug-related adverse events (AEs): peripheral sensory neuropathy, fatigue, decreased appetite, hypoxia, and pneumonitis (n = 1 each). There was 1 drug-related death (hypoxia) (Muro, 2015).

KEYNOTE-028 (NCT02054806) enrolled a cohort (N=23) of esophageal patients with advanced squamous cell carcinoma or adenocarcinoma of the esophagus or GEJ whose tumors were PD-L1 positive (44.6% of evaluable screened patients). Subjects received pembrolizumab 10 mg/kg

every 2 weeks for up to 24 months or until confirmed progression, unacceptable toxicity, or investigator decision. ORR by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 was 30% overall (investigator review). Within the squamous histology group, the ORR was 29% (5 of 17) and ORR was 40% (2 of 5) for subjects with adenocarcinoma. Median time to response was 3.7 months (range 1.8 - 8.3 months) and median duration of response (DOR) was not yet reached (range 5.5 - 11.8+ months) (Doi, 2016).

4.3 Rationale for CRS-207 and Pembrolizumab Immunotherapy in Gastric, Gastroesophageal, and Esophageal Adenocarcinomas

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 including gastric, GEJ, and esophageal adenocarcinomas.

The addition of a checkpoint inhibitor to CRS-207 may enhance the immunotherapeutic potential of these agents by enabling stimulation of targeted immune responses to specific tumor antigens. Nonclinical and clinical studies with CRS-207 to date have demonstrated an acceptable safety profile and evidence of clinical benefit, supported by significant changes in the local tumor microenvironment (unpublished data). [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.

The current study is designed to evaluate whether CRS-207 with pembrolizumab effectively primes specific immune responses and results in clinical benefit for patients with previously treated gastric, GEJ, or esophageal adenocarcinoma. It is hypothesized the expansion of tumor-specific T cells in context of blocking the PD-1/PD-L1 pathway may ultimately provide enhanced anti-tumor efficacy. Although there are no precedent data on the safety of CRS-207/pembrolizumab, CRS-207 is currently being evaluated with the PD-1 inhibitor, nivolumab in an investigator-sponsored Phase 2 study (ADU-CL-06; NCT02243371). The study is evaluating survival, safety and immune response following treatment with CRS-207/GVAX pancreas/cyclophosphamide with or without nivolumab in subjects with previously-treated pancreatic cancer. Initial data from this ongoing clinical study suggests an acceptable tolerability profile of both agents at full dose (nivolumab at 3 mg/kg on Day 1 and CRS-207 1×10^9 CFU on Day 2). These data suggest that a dose escalation phase 1 component in the current study is not required.

For the first cycle, pembrolizumab and CRS-207 will be dosed on consecutive days (pembrolizumab on Day 1 and CRS-207 on Day 2). If Cycle 1 is well tolerated, dosing of both agents will occur on the same day (Day 1) for subsequent cycles. Based on prior clinical experience and expected infusion reactions, it is anticipated that the same-day regimen will be tolerated and more convenient for patients. A Safety Run-in is planned to monitor safety for the first 6 subjects.

4.3.1 CRS-207 Dose Selection Rationale

CRS-207 has been shown to be well-tolerated at the proposed route of administration and dose for this study (Le, 2012). The dose of CRS-207 was chosen based on the Phase 1, dose-escalation study (VAC07001) in which 1×10^9 CFU was determined to be the MTD and shown to be well-tolerated in patients with advanced cancer and induced a mesothelin-specific immune response. The 1×10^9 CFU dose level was also used in the Phase 1B trial (ADU-CL-02) in malignant pleural mesothelioma where initial analysis demonstrates clinical response and acceptable tolerability (Hassan, 2015). CRS-207 dosing at 1×10^9 CFU has been associated with mostly limited and transient infusion-related reactions including rigors/chills, nausea/vomiting, and changes in blood pressure.

The initial CRS-207 dosing regimen (Q3W Cycles 1-4) in this study was designed to synergize with pembrolizumab to optimally prime an immune response. If subjects are clinically stable and/or responding to treatment, CRS-207 infusions will continue every other cycle (Q6W) to sustain the immune response.

4.3.2 Pembrolizumab Dose Selection Rationale

[redacted]

5 STUDY OBJECTIVES

The objectives of the study are to evaluate CRS-207/pembrolizumab when administered to subjects with recurrent or metastatic gastric, GEJ, or esophageal adenocarcinomas with respect to:

- Safety and tolerability
- Tumor response and survival
- Characterization of immune responses, biomarker expression, and molecular characteristics of the tumor microenvironment

6 INVESTIGATIONAL PLAN

6.1 Study Design and Duration

The study is an open-label, single-arm, multicenter clinical study in approximately 79 adults with recurrent or metastatic gastric, GEJ, or esophageal adenocarcinomas who have received one or two prior systemic chemotherapy treatment regimens for advanced disease. Of the approximately 79 evaluable subjects, the study will seek to enroll approximately 50 subjects with gastric/GEJ adenocarcinomas and approximately 29 subjects with esophageal adenocarcinoma to achieve adequate representation of each tumor type.

The study design consists of a 28-day Screening Period, Treatment and Evaluation Period (including a Safety Run-in), and a Follow-up Period. CRS-207 and pembrolizumab will be administered in 3-week cycles. For Cycle 1, pembrolizumab (200 mg) will be administered by IV over 30 minutes on Day 1 and CRS-207 (starting dose 1×10^9 CFU) will be administered IV over 1 hour on Day 2. If the infusions are well tolerated, pembrolizumab and CRS-207 may be administered on the same day (Day 1) for subsequent cycles. After 4 cycles, pembrolizumab will continue to be administered on Day 1 at each treatment cycle (every 3 weeks; Q3W), and CRS-207 will be administered once every 6 weeks (i.e. every other treatment cycle; Q6W). Treatment cycles will continue for up to 24 months as long as there is adequate safety and potential for clinical benefit. If radiographic disease progression is observed, clinically stable subjects who meet dosing eligibility may continue to receive CRS-207 and pembrolizumab according irRECIST guidelines (Section 11). Subjects who experience an unacceptable toxicity directly attributable to either pembrolizumab or CRS-207 may continue on study and receive either pembrolizumab or CRS-207 as single agent study treatment with approval by the Medical Monitor. Alternatively, study drug administration may revert back to consecutive day-dosing regimen as performed in Cycle 1 (Day 1 pembrolizumab and Day 2 CRS-207).

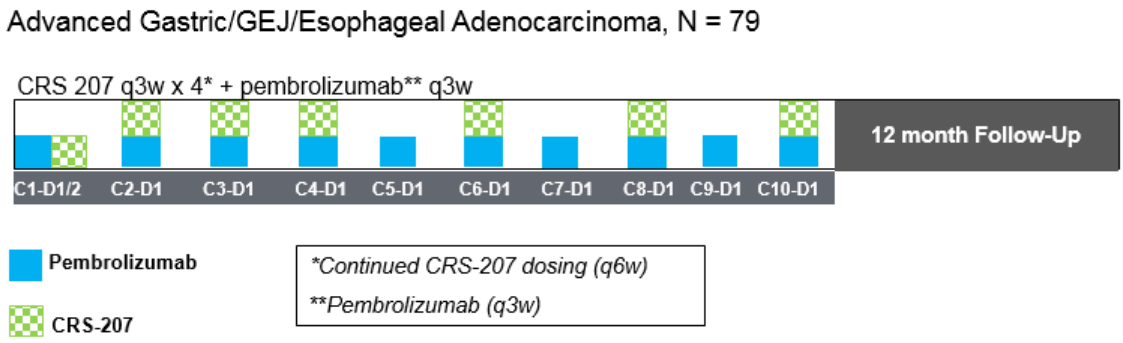
The Treatment and Evaluation Period is defined as the time from Day 1 until discontinuation of both CRS-207 and pembrolizumab, completion of an End-of-Treatment (EOT) Visit, and documented disease progression.

Blood will be collected at EOT to assess clearance of CRS-207 and at [redacted]. The EOT Visit will occur no more than 28 days after the last dose of study drug. If the subject has discontinued CRS-207 but continues on pembrolizumab, the subject will be asked to come back to the clinic [redacted] If the subject begins another anticancer therapy before the end of the 28-day period, all EOT Visit assessments should be completed prior to commencing the new therapy. Unresolved AEs will be monitored until resolution or confirmed stability of the event. Subjects that discontinue all study drugs and complete the EOT without documented progressive disease (based on RECIST v1.1) will be asked to complete Evaluation Visits for tumor imaging every 6 weeks until documented disease progression or start of another anticancer therapy. [redacted]

[redacted]

At the end of the Treatment and Evaluation Period subjects will enter the Follow-up Period of the study and will be followed for survival, subsequent cancer-related therapies, and post treatment monitoring for CRS-207 [redacted] until death or close of study by the Sponsor. The Sponsor may request survival status be assessed at additional time points during the course of the study. Sites will attempt to obtain vital status data 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. Follow-up will continue for at least 12 months from last dose of study drug.

Figure 6-1 ADU-CL-14 STUDY DESIGN



A Safety Run-in will be completed since there are no precedent data on the use of pembrolizumab with CRS-207. Subjects will be monitored for unacceptable toxicity during the first 28 days (through 7 days after the Cycle 2 dose). During the Safety Run-in, evaluable subjects are defined as those who remain on study for the 28-day monitoring period, subjects with unacceptable toxicity, and subjects who are discontinued for safety reasons at the Investigator's discretion (even if criteria for unacceptable criteria are not met). Treatment of the first 6 subjects that are followed for the 28-day period will be staggered with no more than 1 subject treated per week. In the event that 4 in up to 12 safety-evaluable subjects experience an unacceptable toxicity, the subsequent cohort of 12 subjects enrolled will be administered CRS-207 at a dose reduced by a half-log (dose level -1; Table 6-3). In the event of 4 subjects in up to the next 12 safety-evaluable subjects enrolled experience an unacceptable toxicity, the subsequent cohort of 12 subjects enrolled will be administered a reduced dose of CRS-207 (dose level -2; Table 6-3). For each dose reduction (to a minimum of 1×10^8 CFU) the first 12 subjects will be treated and unacceptable toxicities assessed as described above. No adjustments will be made to the pembrolizumab dose.

Safety data and all unacceptable toxicities will be reviewed by a Safety Review Team (SRT) comprised of participating investigators in the study, the Medical Monitor, and Sponsor

representatives. Once the Safety Run-in is complete, safety will continue to be evaluated on an ongoing basis in this open-label study. Cumulative clinical experience with CRS-207 and pembrolizumab will be used to assess whether AEs are considered expected.

The Schedule of Events is provided in Table 1-1. Subjects who experience tolerability issues with same-day dosing may continue to follow the consecutive-day dosing regimen as in Cycle 1 with Day 1 pembrolizumab followed by Day 2 CRS-207 dosing (Table 1-2).

Tumor imaging and evaluation will be assessed at Screening and during the Treatment and Evaluation Period approximately every 6 weeks after initiation of study drug. Tumor measurement and assignment of response will be determined by local Investigators. For subjects on treatment more than 12 months, the frequency of imaging may be reduced to every 12 weeks. Peripheral blood will be collected to assess immune responses directed against *Lm*, mesothelin, and other tumor-associated antigens. Archived tumor tissue and paired tumor biopsies (collected at Screening and during Cycle 2) will be used to explore the association of PD-L1 expression, mesothelin expression, and TIL characteristics with clinical responses.

6.1.1 Discussion of Study Design

The study was designed as a single-arm, open-label, multicenter Phase 2 study. The study is intended to provide the maximum amount of information regarding CRS-207/pembrolizumab safety and tolerability, along with indicators of clinical efficacy and overall survival (OS). Paired tumor biopsies and blood samples will provide an initial investigation into the mechanism of action of this regimen.

For second line patients, standard of care therapies include ramucirumab plus paclitaxel, ramucirumab, paclitaxel or taxanes monotherapies (Mahipal, 2015). In the 3rd line, there is currently no approved therapy for third-line treatment of recurrent or metastatic gastric, GEJ or esophageal adenocarcinomas. Given the life-threatening nature of the disease, a placebo-controlled trial is not appropriate in this setting. Since all subjects will receive the same investigational products, randomization and blinding are unnecessary; study drug will be provided open-label. The study is being conducted as a single-arm trial to evaluate initial safety and efficacy signals before initiating a larger randomized trial.

The study is an exploratory study. The sample size is based on clinical and practical considerations, rather than statistical considerations, and is intended to explore whether the proportion responding to CRS-207/pembrolizumab is similar to or better than what may expected based on data from other clinical studies with checkpoint inhibitors in subjects with recurrent or metastatic gastric, GEJ, or esophageal adenocarcinomas. For reference benchmarks in the second line, ORR ranged from 7% to 28% (Mahipal, 2015). For 3rd line patients, the ORR was 22% for pembrolizumab monotherapy in PD-L1 expressing patients (Muro, 2015).

6.2 Study Population

The population for this study will consist of approximately 79 adults with recurrent or metastatic gastric, GEJ, or esophageal adenocarcinomas who have received one or two prior systemic chemotherapy treatment regimens for advanced disease. Due to overlap in the diagnosis of esophageal, GEJ, and gastric cancers, the study population will consist of adenocarcinomas from all 3 anatomic sites; however, enrollment will be targeted to a minimum of 26 subjects with esophageal cancer (the less prevalent phenotype) to balance the study population. Prior treatment must have included a platinum and a fluoropyrimidine since this is approved therapy and recognized as standard of care in clinical practice. Similarly, eligible subjects must have tumor which are HER-2/neu negative or, if HER-2/neu positive, disease must have previously progressed on treatment with trastuzumab.

Individuals with immunosuppressive disorders or who require immunosuppressive medications will be excluded. An Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and serum albumin levels serve as prognostic indicators of participants more likely to benefit from treatment.

6.2.1 Inclusion Criteria

Individuals eligible to participate in this study must meet all of the following criteria:

1. Aged 18 years or older
2. Diagnosis with confirmed histology (pathology report required) of one or more of the following:
    - Histologically-confirmed gastric or GEJ adenocarcinoma (Siewert type II/III classification)
      [GEJ adenocarcinoma will be defined as primary tumor site within 5 cm proximal and distal of anatomic cardia]

    Or
    - Histologically-confirmed inoperable superior, medial, or distal third esophageal adenocarcinoma (Siewert type I classification may be included, provided there is no mixed histology)
3. Confirmed recurrent or metastatic disease
4. Received and experienced disease progression on, or following one or two prior chemotherapy regimens for advanced disease. Prior treatment must have included a platinum and a fluoropyrimidine.
5. HER-2/neu negative or, if HER-2/neu positive, disease must have previously progressed on treatment with trastuzumab
6. Measurable/assessable disease, as defined by RECIST v1.1. Target lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
7. ECOG performance status of 0 or 1

8. Can provide the following tissue for PD-L1 and mesothelin biomarker analysis:
    - Archived primary tumor tissue (tissue from metastatic site acceptable if archived primary tissue is not available and primary site is not accessible for biopsy)
    - Pre-Treatment biopsy of either primary tumor or metastatic site
    - On-Treatment biopsy at Cycle 2, Day 15
9. Adequate organ and marrow function at Screening, as defined by:

Hematologic	**Renal**	**Hepatic**
WBC ≥ 3000/µL ANC ≥ 1500/µL ALC ≥ 800/µL Platelets ≥ 100,000/µL Hemoglobin ≥ 9 g/dL Albumin ≥ 3.0 g/dL INR or PT ≤ 1.5 × ULN [1] aPTT ≤ 1.5 × ULN [1]	Creatinine ≤ 1.5 × ULN; or measured /calculated creatinine clearance ≥ 60 mL/min if creatinine levels >1.5× ULN	AST/ALT ≤ 2.5 × ULN; or ≤5 × ULN for subjects with liver metastases Total bilirubin ≤ 1.5 × ULN; or ≤ 3 × ULN if due to Gilbert's disease; or direct bilirubin ≤ ULN if total bilirubin > 1.5 × ULN
ALC = absolute lymphocyte count; ALT = alanine aminotransferase; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; INR = international normalized ratio PT = prothrombin time; ULN = institutional upper limit of normal; WBC = white blood cell [1] If receiving anticoagulant therapy, values should be within therapeutic range of intended use		

Any Grade 3 or higher abnormality in any serum chemistry or hematology parameter should be discussed and approved by the Medical Monitor prior to enrollment (even if considered not clinically significant)

10. Women of childbearing potential (WOCBP) and fertile males with WOCBP partners must use highly effective contraception (CTFG, 2014) throughout the Treatment and Evaluation Period (from first dose and through 120 days after final dose of study drug). Contraception must include at least one barrier method to minimize risk of fluid transmission.
11. Provide written informed consent and is willing and able to comply with all study procedures.

6.2.2 Exclusion Criteria

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

1. Diagnosis of squamous or undifferentiated gastric cancer
2. Individuals with inaccessible tumors or for whom biopsy is contraindicated
3. Participated in any other study in which receipt of an investigational new drug or investigational device occurred within 28 days of first dose of study drug
4. Diagnosis of immunodeficiency, receiving TNF pathway inhibitors, PI3 kinase inhibitors, chronic systemic steroid therapy (> 10 mg/day of prednisone or equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug
5. Clinical evidence of ascites by physical exam

6. Prior anti-cancer monoclonal antibody within 4 weeks prior to first dose of study drug or has not recovered from adverse effects due to agents administered more than 4 weeks earlier
7. Prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to first dose of study drug, or has not recovered from adverse effects (i.e. ≤ Grade 1 or baseline) from adverse effects due to a previously-administered agent

   Note: Subjects with ≤ Grade 2 neuropathy or ≤ Grade 2 alopecia are an exception to this criterion.
8. Active second malignancy with the exception of any of the following:
   - Adequately treated basal cell carcinoma
   - Squamous cell carcinoma of the skin, or in situ cervical cancer
   - Low-risk prostate cancer (i.e. Gleason score < 7 and prostate specific antigen < 10 ng/mL); or
   - Any other cancer from which the individual has been disease-free for ≥ 3 years
9. 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.
10. Active infection requiring systemic therapy
11. Known **active** central nervous system metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging at least 4 weeks prior to the first dose of study drug and neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to first dose of study drug. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.
12. History of (non-infectious) pneumonitis that required steroids, or current pneumonitis
13. History of interstitial lung disease
14. Prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent, or agents targeting other checkpoint pathways (e.g. CTLA-4, LAG-3, GITR, OX40), or prior participation in Merck MK-3475 clinical trials
15. Prior immunotherapy with CRS-207 or any other *Listeria*-based agent, therapeutic cancer vaccine, or adoptive T cell immunotherapy
16. Major surgery or significant traumatic injury occurring within 28 days prior to first dose of study drug

    Note: If major surgery occurred > 28 days prior to first dose of study drug, individual must have recovered adequately from the toxicity and/or complications from the intervention prior to first dose of study drug
17. Previous treatment with >2 systemic chemotherapy regimens for advanced disease
18. Known allergy to <u>both</u> penicillin and sulfa antibiotics

19. Unable or unwilling to withhold or discontinue any prohibited or restricted medications/procedures/immunizations for the specified windows during the study
20. If WOCBP, pregnant or breastfeeding; negative pregnancy status must be confirmed within 24 hours of first dose of study drug
21. Known valvular heart disease that requires antibiotic prophylaxis for prevention of endocarditis
22. Clinically significant heart disease (such as uncontrolled angina, myocardial infarction within 3 months of study initiation, congestive heart failure, or New York Heart Association Class III or IV heart failure)
23. History of autoimmune disease that has required systemic treatment in the past 2 years, including:
    - 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)

    Note: Individuals with vitiligo, Sjogren's syndrome, interstitial cystitis, Graves' or Hashimoto's Disease, celiac disease, diabetes mellitus type 1, or hypothyroidism stable on hormone replacement will be allowed with Medical Monitor approval.
24. Intercurrent illness that is either life-threatening or of clinical significance such that it might limit compliance with study requirements or in the Investigator's assessment would place the subject at an unacceptable risk for study participation;
25. Received a diagnosis of human immunodeficiency virus (HIV)
26. Received a diagnosis of hepatitis B, or hepatitis C for which there is no clear evidence of natural immunity, immunity subsequent to vaccination, or successful eradication of the virus following antiviral therapy (individuals who are hepatitis C antibody positive may be enrolled if negative viral load confirmed at screening)
27. Subjects who have who have implanted medical devices that pose high risks for colonization and cannot be easily removed (e.g., artificial heart valves, pacemakers, prosthetic joints, orthopedic screw(s), metal plate(s)) if infection occurs. Other common devices such as venous access devices (e.g., Port-a-Cath or Mediport) may be permitted as well as arterial and venous stents and dental and breast implants that were placed more than 3 months prior to first dose of study drug.
28. Prior severe hypersensitivity (≥ Grade 3) to CRS-207, pembrolizumab, or any study drug excipients (e.g. yeast, glycerol)
29. Unhealed wound
30. History or evidence of inherited bleeding diathesis or coagulopathy

31. Received any prophylactic vaccine within 14 days of first dose of study drug or received a live vaccine within 30 days of planned start of study therapy. Seasonal flu vaccines that do not contain a live virus are permitted.

6.2.3 Dosing Eligibility and Delayed Dosing

Subjects must have adequate organ function confirmed (as defined by the laboratory values in Table 6-1) prior to each dosing cycle where CRS-207 is administered; laboratory tests may be performed up to 3 days before dosing.

Table 6-1 Dosing-Eligibility Requirements

Hematologic	Renal	Hepatic
WBC ≥ 3000/μL ANC ≥ 1000/μL Platelets ≥ 90,000/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 = institutional upper limit of normal; WBC = white blood cell		

Subjects who do not meet dosing eligibility requirements will be monitored; 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 Medical Monitor for further instruction on continued dosing.

Pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons. If subjects on same-day dosing schedule experience severe infusion-related reactions related to the pembrolizumab infusion, the CRS-207 infusion may be delayed to Day 2. CRS-207 must be administered one day after pembrolizumab administration. If the subject experiences a new AE or is recovering from an AE, CRS-207 administration may be delayed up to 7 days and 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.

Dosing interruptions are 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). 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.

6.2.4 Subject Discontinuation

Subjects will be encouraged to complete the study; however, they may voluntarily withdraw from treatment or the study at any time. The Investigator will provide a written explanation describing the reason for discontinuation from treatment or study in a source document, which will be entered into the electronic case report form (eCRF). Subjects who discontinue treatment

will complete the EOT assessments, [redacted] and post-treatment monitoring for CRS-207. Subjects will be encouraged to participate in the Follow-up Period. 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 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 lost to follow up.

A subject in this clinical study may be discontinued from treatment for any of the following reasons:

- The subject withdraws consent or requests discontinuation for any reason
- Occurrence of any medical condition or circumstance that exposes the subject to substantial risk and/or does not allow the subject to adhere to the requirements of the protocol
- Any serious adverse event (SAE), clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition which indicates to the Investigator that continued participation is not in the best interest of the subject
- Pregnancy
- Subject failure to comply with protocol requirements or study-related procedures
- Termination of the study by the Sponsor or the regulatory authority

Subjects who experience an unacceptable toxicity directly attributable to either pembrolizumab or CRS-207 may continue on study and receive either pembrolizumab or CRS-207 as single agent treatment following completion of the Sponsor Consultation Form and approval by the Medical Monitor. Alternatively, study drug administration may revert back to consecutive day-dosing regimen as performed in Cycle 1.

6.2.4.1 Stopping Rules

Subjects will be monitored throughout the study for unacceptable toxicity (Section 6.3.1.1); provisions are in place for a Safety Run-in, CRS-207 dose reductions, dose modifications, and continuation on either CRS-207 or pembrolizumab as a single agent. The following safety rules will apply to the study to further mitigate potential risk to subjects:

- Grade 5 toxicity (death) in any subject within 30 days of receipt of study drug(s) unless clearly related to an alternative cause other than study drug
- Unacceptable toxicity occurring in >33% of subjects dosed with CRS-207/pembrolizumab

Should these events occur the SRT will evaluate available data within 72 hours of notification of the event(s) and recommend whether to stop the study, suspend dosing and/or enrollment, or determine whether additional dose adjustments are warranted.

6.3 Study Treatments and Additional Medications

Subjects will receive the assigned treatment course described in Table 6-2.

Table 6-2 ADU-CL-14 Study Treatment Course

Study Drug	Dose / Route	Treatment Course
Pembrolizumab	200 mg administered IV over 30 min (-5 min/+10 min)	Day 1 of each cycle
CRS-207	1×10^9 CFU administered IV over ~ 1 hour	Day 2 of Cycle 1 Day 1 of Cycle 2, 3, 4; Q6W thereafter [1]

CFU = colony-forming unit; IV = intravenous; Q6W = every 6 weeks

[1] Subjects who experience tolerability issues may continue to follow the consecutive-day dosing regimen as in Cycle 1 and follow the Schedule of Events for Consecutive Day Dosing (Table 1-2).

6.3.1 Safety Run-In Period

A Safety Run-in will be completed since there are no precedent data on the use of pembrolizumab with CRS-207. Subjects will be monitored for unacceptable toxicity during the first 28 days (through 7 days after the Cycle 2 dose). During the Safety Run-in, evaluable subjects are defined as those who remain on study for the 28-day monitoring period, subjects with unacceptable toxicity, and subjects who are discontinued for safety reasons at the Investigator's discretion (even if criteria for unacceptable criteria are not met). Treatment of the first 6 subjects that are followed for the 28-day period will be staggered with no more than 1 subject treated per week. In the event that 4 in up to 12 safety-evaluable subjects experience an unacceptable toxicity, the subsequent cohort of 12 subjects enrolled will be administered CRS-207 at a dose reduced by a half-log (dose level -1). In the event of 4 subjects in up to the next 12 safety-evaluable subjects enrolled experience an unacceptable toxicity, the subsequent cohort of 12 subjects enrolled will be administered a reduced dose of CRS-207 (dose level -2). For each dose reduction (to a minimum of 1×10^8 CFU) the first 12 subjects will be treated and unacceptable toxicities assessed as described above. No adjustments will be made to the pembrolizumab dose. The dose levels and dose reduction permutations are provided in Table 6-3.

Table 6-3 Safety Run-in Dose Levels and Dose Reduction Plan

Dose level	Pembrolizumab	CRS-207
1	200 mg	1×10^9 CFU
-1	200 mg	3×10^8 CFU
-2	200 mg	1×10^8 CFU

6.3.1.1 Unacceptable Toxicities

The unacceptable toxicity criteria will be any of the following unless clearly related to an alternative cause other than study drug:

- Grade 5 toxicity
- Grade 4 non-hematologic toxicity (not laboratory)
- Grade 4 hematologic toxicity lasting ≥7 days
- Grade 3 non-hematologic toxicity (not laboratory) lasting >3 days despite optimal supportive care
- Any Grade 3 or Grade 4 non-hematologic laboratory value if:
  - Medical intervention is required to treat the subject,
    or
  - The abnormality leads to hospitalization, or
  - The abnormality persists for >1 week
- Grade 3 or 4 febrile neutropenia
  - Grade 3 is defined as ANC <1000/mm^3 with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than one hour
  - Grade 4 is defined as ANC <1000/mm^3 with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than one hour, with life-threatening consequences and urgent intervention indicated
- Thrombocytopenia <25,000/mm^3 if associated with:
  - A bleeding event which does not result in hemodynamic instability but requires an elective platelet transfusion,
    or
  - A life-threatening bleeding event which results in urgent intervention and admission to an Intensive Care Unit
- Delay of >8 days starting Cycle 2 due to study drug-related toxicity
- Administration of systemic steroids to treat an immune-mediated reaction
- Serum chemistry laboratory values consistent with Hy's Law criteria (i.e. all 3 of the following must coexist):
  - ALT or AST ≥ 3 × ULN
  - Total bilirubin ≥ 2 × ULN
  - ALP < 2 × ULN

Safety data and all unacceptable toxicities will be reviewed by the SRT comprised of participating investigators in the study, the Medical Monitor, and Sponsor representatives. Once the Safety Run-in is complete, safety will continue to be evaluated on an ongoing basis in this open-label study. Cumulative clinical experience with CRS-207 and pembrolizumab will be used to assess whether AEs are considered expected.

Subjects who experience an unacceptable toxicity directly attributable to either pembrolizumab or CRS-207 may continue on study and receive either pembrolizumab or CRS-207 as single agent treatment following completion of the Sponsor Consultation Form and approval by the Medical Monitor. Alternatively, study drug administration may revert back to consecutive day-dosing regimen as performed in Cycle 1.

6.3.2 Method of Assigning Subjects to Treatment

All subjects will be sequentially assigned a unique subject identification number upon providing informed consent. The study is designed as a single-arm study; all subjects will receive CRS-207/pembrolizumab as indicated.

6.3.3 Blinding

ADU-CL-14 is a single-arm, open-label study. Due to the expected infusion-related reactions and required pre-medications associated with CRS-207 administration, and since all subjects receive the same study drugs, it is not feasible or necessary to conduct the study under blinded conditions. All study treatments will be administered open-label; no study participants or site personnel will be blinded to study treatment.

6.3.4 Investigational Product: CRS-207

CRS-207 is a LADD strain 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 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. CRS-207 is stored frozen at -60 ºC or colder until just before IV administration. CRS-207 is supplied by the Sponsor. Additional information on CRS-207 may be found in the Pharmacy Manual and IB.

6.3.4.1 Biosafety and 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 (Brockstedt, 2004).

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* (BVL, 1999). 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.

6.3.4.2 CRS-207 Administration

CRS-207 is intended for IV administration. The intended dose of CRS-207 is 1×10^9 CFU diluted in sterile saline and administered by IV infusion. 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) 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 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 date when 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 maximum dose permitted by label) acetaminophen (paracetamol). Adequate hydration is important to mitigate infusion-related reactions. All subjects are required to receive a minimum of 0.5 L 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. For Same-day dosing on Cycle 2 only, observe subjects for at least 4 hours. For all subsequent infusions observe subjects for at least 2 hours post infusion. Subjects should continue to be monitored after infusion and released once they are considered clinically stable. Vital signs and pulse oximetry will be monitored (Section 6.4.3.1). Presence of fever alone in the absence of other clinical signs and symptoms 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.

During and after CRS-207 infusions, subjects may experience fever, chills/rigor, blood pressure changes, nausea, and vomiting. Refer to Section 6.3.7 and the IB for additional details on CRS-207 administration and supportive care.

6.3.4.3 CRS-207 Dose Modification

CRS-207 at the proposed dose level has been well tolerated and dose reductions are not anticipated. However, in the event of AEs of concern that are attributable to CRS-207 the Medical Monitor should be contacted; the dose of CRS-207 may also be modified outside the Safety Run-in Period as warranted on an individual basis.

6.3.5 Investigational Product: Pembrolizumab

Pembrolizumab is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is an IgG4 kappa immunoglobulin with an approximate molecular weight of 149 kDa. Pembrolizumab is not currently approved for treatment of gastric, GEJ, or esophageal adenocarcinomas 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.

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.

6.3.5.1 Pembrolizumab Administration

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 Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion and administration of infusion solution.

Pembrolizumab Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the investigator. Suggested supportive care measures for the management of pembrolizumab-related AEs with potential immunologic etiology along with dose modification guidelines are outlined below. Where appropriate, these guidelines include the use of oral or IV treatment with

corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the Investigator determines the events to be related to pembrolizumab.

Note: If the event is determined not to be related to pembrolizumab, the Investigator does not need to follow the treatment guidance (as outlined below). It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

6.3.5.2 Pembrolizumab Dose Modification and Toxicity Management

Immune-related Adverse Events Associated with Pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical trial data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids.

Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 6-4. The Medical Monitor will be consulted regarding continued dosing of CRS-207 should any of these events occur. During the Safety Run-in Period withholding pembrolizumab or administering systemic steroids would define an unacceptable toxicity.

Table 6-4 Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events Associated with Pembrolizumab

General Instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2mg/kg prednisone or equivalent) followed by taper	• Monitor subjects for signs and symptoms of pneumonitis • Evaluate subjects with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent grade 2	Permanently discontinue		
Diarrhea / colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2mg/kg prednisone or equivalent) followed by taper	• Monitor subjects for signs and symptoms of enterocolitis (i.e. diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e. peritoneal signs and ileus). • Subjects with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Subjects with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		

AST / ALT elevation or Increased Bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for subjects with T1DM • Administer anti-hyperglycemic in subjects with hyperglycemia	• Monitor subjects for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (e.g. propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or Permanently discontinue1		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (e.g. levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		

All Other immune-related AEs	Grade 3, or intolerable/ persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 4 or recurrent Grade 3	Permanently discontinue		

NOTES:

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.
2. For subjects with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

Infusion Reactions Related to Pembrolizumab

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 6-5.

Table 6-5 Pembrolizumab Infusion Reaction Dose Modification and 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 therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** 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 1 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 study drug treatment	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (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: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids 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. **In cases of anaphylaxis, epinephrine should be used immediately. **Subject is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

Other Allowed Dose Interruptions for Pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. 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.

6.3.6 Antibiotics

To eliminate any potentially residual CRS-207, subjects will be administered antibiotics at the EOT visit or 7 days after the last dose of CRS-207 (for patients continuing on pembrolizumab), prior to receiving subsequent cancer-related (non-study) therapy. [redacted]

[redacted]

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

6.3.6.1 Suspected Infection with CRS-207

Suspected infection with CRS-207 and/or Listeria is considered an adverse event of special interest (AESI; Section 7.3.5) and should be reported following SAE reporting procedures (Section 7.3) irrespective of temporal relationship to study drug administration. This includes scheduled blood cultures during surveillance monitoring that are positive for CRS-207 or if a subject presents with symptoms suspicious for a Listeria-like infection and/or is tested positive for Listeria at a local hospital/clinic.

In the case of suspected persistent CRS-207 or Listeria infection, blood, urine and stool samples should be obtained in duplicate. One set of samples should be cultured locally for Listeria per institutional guidelines. Culture of cerebrospinal fluid should be obtained for subjects with suspected central nervous system infection. In such instances, analysis of cerebrospinal fluid should also include cell count, protein, glucose, and Gram stain. If samples are positive for Listeria, the Sponsor must be notified immediately, and the duplicate samples and Listeria isolate must be sent for testing to confirm CRS-207. Instructions on collection, storage and shipping of samples for CRS-207 testing are provided in the Laboratory Manual

If infection with CRS-207 is confirmed or suspected, IV antibiotics (see below) should be initiated as soon as possible and follow-up cultures obtained periodically to confirm absence/clearance of any CRS-207 infection. The Medical Monitor should be consulted regarding continuation of study drug treatment and treatment of suspected or confirmed infection.

Antibiotic Treatment for CRS-207 Infection

[redacted]

[redacted]

6.3.7 Concomitant Medications and Procedures

Subjects may receive concomitant medications as required, unless specifically restricted or prohibited in this study (Section 6.3.8). Minor procedures such as dental work, skin biopsy, celiac plexus block, biliary stents, mediport/port insertion, and video-assisted thoracic surgery biopsy are allowed; however, CRS-207 should not be administered within 14 days of the procedure or until the investigator determines there is no additional risk to the subject.

During the course of the study, subjects are anticipated to continue the use of prescribed medications identified during the screening procedures, consistent with study inclusion and exclusion criteria.

Concomitant medications used in this study include:

- Acetaminophen (paracetamol) prior to each CRS-207 infusion
- Antiemetics according to American Society for Clinical Oncology guidelines (Basch, 2011)
- Antipyretics to treat fever or to prevent recurrence of fever post-CRS-207 infusion
- IV narcotics such as morphine or meperidine (per institutional policy) for rigors associated with CRS-207 dosing
- 7-day antibiotic regimen following last dose of CRS-207

6.3.8 Prohibited Medications and Procedures

A subject may be removed from the study for use of prohibited medications or procedures. Approval must be obtained from the Medical Monitor for a subject to continue dosing if a prohibited medication is administered within the specified timeframes. The following therapies are not permitted or restricted during the study:

- Non-study chemotherapy or immunotherapy (approved or investigational)
- TNF pathway inhibitors or PI3 kinase inhibitors
- Palliative radiation
- Live vaccines (examples of live vaccines include, but are not limited to: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid [oral] vaccine). Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Any major surgery or surgical procedure; if required must be discussed with the Medical Monitor to determine if it is appropriate for the subject to continue study treatment
- Any other investigational product

If a subject requires an emergent implant of a prohibited device while on therapy, the subject will receive a 14-day IV antibiotic regimen (Section 6.3.6.1).

In addition, the following medications are only restricted prior to and after CRS-207 infusions as indicated:

- Systemically active steroids for more than 3 days or use of any systemic steroids within 14 days before or after CRS-207 infusion, with the exception of inhaled and topical steroids
- Filgrastim (granulocyte colony stimulating factor; G-CSF) or sargramostim (granulocyte-macrophage colony stimulating factor; GM-CSF) within 14 days prior to or 14 days after CRS-207 infusion
- Prophylactic vaccines (e.g. pneumococcal vaccine, influenza vaccine) within 14 days prior to or after CRS-207 infusion

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

- General anesthesia or deep sedation
- Aspirin >325 mg/day
- Acetaminophen > 4 g/day
- Systemic antibiotics

There are no prohibited therapies during the Follow-up Period.

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).

6.3.9 Treatment Compliance

Study treatments will be administered by IV infusion by a qualified health care professional at an approved study site. The date, time, and volume of each dose of study drug administered to each subject must be recorded in the dispensing log for the study and the eCRF.

Antibiotics will be provided to subjects following the last dose of CRS-207 as indicated in Table 1-1 or Table 1-2. Site personnel will contact the subject by telephone to facilitate compliance with antibiotic treatment; subjects will be required to record self-administration of antibiotics in a diary.

6.4 Study Assessments and Procedures

Screening assessments will be conducted to confirm eligibility and to obtain baseline measurements; screening must be completed within 28 days prior to first dose of study drug. An

enrollment form will confirm subject eligibility after completion of all screening procedures. Subjects must initiate dosing of study drugs within 2 weeks of completed enrollment.

Subjects will be requested to complete multiple clinic visits during the initial four dosing cycles; visit frequency is reduced beginning at Cycle 4 and beyond. An EOT Visit will occur within 28 days after the last dose of study drug. If the subject begins another anticancer therapy before the end of the 28-day period, all EOT Visit assessments should be completed prior to commencing the new therapy. Unresolved AEs will be monitored until resolution or confirmed stability of the event.

After the EOT Visit, subjects will be followed [redacted] to collect data on survival, CRS-207 monitoring, and any subsequent cancer-related therapies until death or close of study by the Sponsor. Sites will attempt to obtain vital status data 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. Follow-up will continue for at least 12 months from last dose of study drug.

All study visits (and visit windows), assessments, and procedures will be performed as indicated in the Schedule of Events (Table 1-1 or Table 1-2). Further details of study procedures and assessments can be found in the Study Reference and Laboratory Manuals.

6.4.1 General Assessments

6.4.1.1 Informed Consent

Before screening assessments are conducted, an individual must be given a complete explanation of the purpose and requirements of the study; an informed consent form (ICF) approved by the Institutional Review Board (IRB)/Ethics Committees (EC) and an authorization for use and disclosure of protected health information must be signed before any study-specific procedure is performed. However, assessments done as part of standard of care prior to informed consent 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; a copy will be provided to the subject.

6.4.1.2 Demographics, Medical History, and Height

Demographic data and a complete medical history will be collected at screening by the Investigator or qualified designee. Demographic information (as allowed by local regulations) will include date of birth, age, gender, ethnicity, and race. 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 surgery(ies), radiation therapy, and stage of cancer) will be recorded.

Height (without shoes) will be obtained at screening with a stadiometer. Body mass index will be derived using height and weight.

6.4.1.3 Archived Tumor Tissue and Tumor Biopsies

Archived tissue from the primary tumor will be collected for all enrolled subjects to assess expression of PD-L1 and mesothelin by immunohistochemistry (IHC). Archived samples should be submitted with a pathology report; personal identifying information must be redacted. If archival primary tumor tissue from the original diagnostic formalin-fixed paraffin-embedded block is not available, tissue from metastatic site is acceptable if primary site is not accessible for biopsy.

Paired tumor biopsies of primary tumor or a metastatic site for pre-treatment and on Cycle 2 Day 15 will be collected to evaluate changes in PD-L1 and mesothelin status, as well as any cellular or genomic changes in markers of immune response or disease status. If at Cycle 2 a subject's tumor is thought to be unsafe for biopsy by the Investigator, the site must discuss with the Medical Monitor to determine if an alternative acceptable method may be allowed.

An image assisted core needle biopsy using standard techniques will be obtained from the primary tumor site(s) and/or accessible metastatic lesions. The tissue sample should have proper size to enable IHC analysis of PD-L1 and mesothelin. Fine needle aspirations will not be acceptable.

Paired biopsies will be collected 1) any time between screening and prior to the first dose of study medication (baseline) and 2) during treatment (Cycle 2 Day 15 post CRS-207/pembrolizumab administration). Cycle 2 Day 15 biopsy should not be collected until at least seven (7) days have passed since CRS-207 administration, but no later than Day 15 of cycle to allow sufficient recovery time prior to CRS-207 administration. An additional biopsy may be requested at the EOT visit. 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. Detailed instructions for tissue collection, processing and shipment are provided in the Laboratory Manual.

6.4.1.4 Eligibility

Potential subjects will be evaluated for entry into the study according to the stated inclusion and exclusion criteria (Section 6.2). Individuals deemed ineligible for study enrollment do not need to complete all screening procedures. The reason for ineligible status will be documented. 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).

For subjects who meet all inclusion/exclusion criteria, an enrollment form will be completed and sent to Sponsor or designee for review and approval. All screening assessments must be completed within a 4-week (28 day) period; treatment must be initiated within 2 weeks of approved enrollment.

6.4.2 Efficacy Measures

Efficacy will be evaluated by changes in tumor burden and survival. The assessments that will be performed throughout the study to derive primary, secondary, and exploratory efficacy variables are described below and will be conducted according to the Schedule of Events (Table 1-1 or Table 1-2). Efficacy endpoints and associated analyses are described in Section 6.5.5.

6.4.2.1 Tumor Imaging and Response Assessments

Computed tomography (CT) scans of the chest, abdomen and pelvis will be performed at screening (pre-treatment baseline assessment) within 28 days of first dose of study drug and at approximately 6 week intervals after initiation of study drug using the same assessment technique. If CT scan is contraindicated (e.g. allergy to contrast dye), magnetic resonance imaging (MRI) should be performed. Subjects with previously treated brain metastases must be stable (without evidence of progression by imaging at least 4 weeks prior to the first dose of study drug and neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases. Radiographic tumor evaluation should include CT of all affected sites.

For each scan, tumor measurements should be obtained using RECIST v1.1 and assessment of response determined by the local Investigator. The investigator/local radiology review will also use irRECIST (Section 11) to assess tumor response and progression, and make treatment decisions. If radiographic disease progression is observed, another scan should be done at least four weeks later to confirm disease progression prior to treatment discontinuation. Subjects discontinued after confirmation of progression will enter the Follow-Up Period. Subjects that discontinue all study drugs and complete the EOT without documented progressive disease (based on RECIST v1.1) will be asked to complete tumor imaging every 6 weeks until documented disease progression or start of another anticancer therapy.

The method of assessment and technique should be consistent throughout the study to enable characterization of each identified and reported lesion.

For subjects on treatment more than 12 months, the frequency of imaging may be reduced to every 12 weeks.

6.4.2.2 Survival Follow-Up

Following the Treatment and Evaluation Period, subjects will be contacted at 12 [redacted] to assess survival and subsequent cancer-related therapies. A telephone contact should also be scheduled at least 90 days post-treatment discontinuation to satisfy reporting requirements for SAEs and events of clinical interest.

Follow-up will continue until death of the subject, loss to follow-up, or close of study by the Sponsor. For subjects who withdraw from the study prior to completion of the Follow-up Period, reasonable efforts will be made to collect survival outcome. Sites will attempt to obtain vital

status data 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. All deaths must be reported on the eCRF.

The Sponsor may request survival status be assessed at additional time points during the course of the study. These additional contacts may be requested for safety review, interim analysis, and/or final analysis. All subjects who are not known to have died prior to the request for these additional survival status time points will be contacted at that time.

6.4.3 Safety Assessments

Safety assessments will be performed to characterize the safety of CRS-207/pembrolizumab use in patients with gastric, GEJ, or esophageal adenocarcinomas. Safety will be assessed by collection of data on parameters including SAEs, TEAEs, infusion-related reactions, ECOG performance status, vital sign measurements, standard clinical laboratory parameters (serum chemistry, hematology, coagulation, thyroid function, and urinalysis), and electrocardiogram (ECG) parameters. Clinically significant changes from pre-treatment values in safety assessments should be reported as AEs. Safety assessments described below will be conducted according to the Schedule of Events (Table 1-1 or Table 1-2).

6.4.3.1 Eastern Cooperative Oncology Group Scale of Performance Status

The ECOG Scale of Performance Status is recognized as a standard tool to measure disease impact on daily living activities (Oken, 1982). 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).

6.4.3.2 Vital Signs and Pulse Oximetry

Vital signs, including blood pressure, pulse rate, respiratory rate, and temperature will be performed at each indicated study visit. Vital signs and pulse oximetry will be obtained prior to, and immediately following each pembrolizumab infusion. Vital signs and pulse oximetry will be obtained prior to and every 30 minutes during CRS-207 infusion, and every hour during post-infusion follow-up.

Any clinically significant abnormal findings in vital signs, pulse oximetry, or weight should be recorded as an AE.

6.4.3.3 Physical Examination and Weight

Comprehensive Physical Examination

Complete physical examinations will be conducted at screening and EOT. Comprehensive 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 AEs.

Symptom-directed Physical Examination

Symptom-directed physical examinations will be conducted at all other indicated visits (up to 3 days prior to dosing). 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, AEs, or other findings. New clinically significant abnormal findings should be recorded as AEs.

Weight

Weight will be obtained at each indicated visit, and prior to receiving any study medication.

6.4.3.4 Adverse Events

AEs will be recorded from the time of first study drug administration until 28 days following the last dose of study drug or initiation of subsequent cancer-related therapy, whichever occurs first. SAEs should be reported per the timeframe and procedures described in Section 7.3. If the EOT visit occurs less than 28 days from the last dose of study drug, the subject will be contacted by telephone 28 days (+ 3 days) after the date of last study drug administration to complete the AE reporting period. A follow-up contact for AEs will also be conducted 1 day after each CRS-207 infusion (and one day after pembrolizumab infusions beyond Cycle 5 where CRS-207 is not administered). Contact must be documented in the study records.

All AEs and abnormal clinical laboratory assessments will be assessed for severity using the NCI-CTCAE v. 4.03. The determination, evaluation, reporting, and follow-up of AEs will be performed as outlined in Section 7.

6.4.3.5 Concomitant Medications

Medications used within 28 days prior to first dose of study drug will be recorded. A telephone follow-up for concomitant medications will also be conducted 1 day after each CRS-207 infusion (and one day after pembrolizumab infusions during Cycle 5 and beyond where CRS-207 is not administered). All concomitant medication administered from the first study drug administration until the EOT visit will be recorded in the eCRF (including pre-medications and all over the counter medications). The generic name, dosage, duration, and reason for the concomitant medication should be included. Changes in the use of concomitant medications will be captured at each study visit.

6.4.3.6 Electrocardiogram

At indicated visits routine 12-lead ECGs will be performed. ECGs should be performed after the subject has rested for ≥5 minutes.

For consecutive-day dosing, ECGs will be performed prior to each dose of study medication, immediately after the infusion, and at 1-hour post infusion. For visits where pembrolizumab and CRS-207 are administered consecutively (Day 1 and Day 2), routine 12-lead ECGs will be performed prior to each infusion, immediately after each infusion, and at 1-hour post infusion. For visits where pembrolizumab and CRS-207 are administered on the same day, routine 12-lead ECGs will be performed prior to pembrolizumab infusion, immediately after pembrolizumab infusion, immediately after CRS-207 infusion, and at 1-hour post CRS-207 infusion. If abnormal at 1-hour post-infusion, repeat until baseline achieved. Additional ECGs may be performed if clinically indicated.

ECG parameters include heart rate, PR interval, QT interval, QRS duration, QTcF (Fridericia's correction), and QTcB (Bazett's correction). The ECG will be interpreted by the Investigator as normal, not clinically significant abnormal, and clinically significant abnormal results. Clinically significant abnormal findings should be recorded as an AE.

6.4.3.7 Clinical Laboratory Evaluation for Safety

Routine hematology, serum chemistry, and urinalysis will be performed as a safety measure and to confirm dosing eligibility throughout the study (Section 6.4.4.2). The clinical significance of laboratory parameter findings will be determined by the Investigator throughout the study. The 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. 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. All abnormal laboratory values considered clinically significant by the Investigator must be recorded in the AE page of the eCRF. Any abnormal test that is determined to be an error does not require reporting as an AE.

6.4.4 Laboratory Assessments

A panel of laboratory assessments on blood and urine samples will be used to characterize the study population, and assess efficacy and safety throughout the Treatment and Evaluation Period. Assessments will be conducted per the Schedule of Events (Table 1-1).

6.4.4.1 Screening/Baseline-specific Laboratory Assessments

Blood samples will be obtained at screening to confirm eligibility and characterize immune status and prognostic tumor biomarkers for each subject and the study population. These initial laboratory assessments may be conducted at the local laboratory and include:

- Virology screen for HIV antibody, hepatitis B surface antigen, and hepatitis C antibody
    - Hepatitis C viral load (if indicated)

6.4.4.2 Safety Laboratory Assessments

Routine hematology, serum chemistry, thyroid function tests, coagulation panels, and urinalysis will be conducted as a measure of safety and dosing eligibility per protocol requirements (Section 6.2.3). All clinical laboratory evaluations will be performed by the institution's local laboratory. Testing may be completed up to 3 days prior to each study drug administration. Fasting is not required. Additional tests may be performed if clinically indicated.

The following parameters will be evaluated at Screening and throughout the Treatment and Evaluation Period as indicated:

- Thyroid panel: triiodothyronine (T3) or free triiodothyronine (FT3), free thyroxine (FT4), thyroid stimulating hormone (TSH)
- Hematology: complete blood count (WBCs, red blood cells, hematocrit, and hemoglobin) with differential including absolute neutrophil count, absolute lymphocyte count, and platelet count
- Serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, lactate dehydrogenase, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin (total, direct, indirect), total protein, albumin, calcium, magnesium, uric acid, and phosphate
- Coagulation panel: prothrombin time, international normalized ratio of prothrombin time, activated partial thromboplastin time, and D-dimers, fibrinogen
- Urinalysis: bilirubin, blood, glucose, ketones, leukocytes, nitrite, pH, protein, and specific gravity (includes microscopy at Screening and EOT)

Pregnancy Testing and Contraception

The effects of CRS-207 and pembrolizumab on a fetus *in utero* or on the composition of sperm are unknown. Therefore, WOCBP and fertile males must consent to use highly effective contraception (CTFG, 2014) from the first dose through 120 days after their final dose of study drug. Contraception must include at least one barrier method to minimize risk of fluid transmission. Sexual abstinence is an acceptable method of contraception; if abstinence is employed, use of barrier method is not applicable.

A WOCBP is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. For study eligibility, WOCBP must have negative pregnancy tests at screening and within 24 hours of first study drug administration. A serum pregnancy test (human chorionic gonadotropin) is required at screening; at all other indicated visits, only a urine pregnancy test is required. If a urine pregnancy test is positive, the

results should be confirmed with a serum pregnancy test. Pregnancy of a subject or partner must be reported and followed (Section 7.4).

6.4.4.3 Biomarker and Research Laboratory Assessments

Research assessments conducted on blood samples and tumor tissues may help to characterize and monitor baseline and post-treatment immune responses mediated by CRS-207 and pembrolizumab. Samples required for laboratory evaluations will be collected and processed by sites as outlined in the Laboratory Manual. All analyses will be conducted by the Sponsor or the Sponsor's designee.

Biomarker and research laboratory assessments may include:

- Total CD4 and CD8 counts
- Human leukocyte antigen (HLA) typing (type A and B of MHC Class I antigens; intermediate resolution)
- Characterization of treatment induced humoral and cellular immune responses including T cell responses to *Lm* and mesothelin
- Immune cellular phenotyping and functional analyses of peripheral blood mononuclear cells (PBMCs) and TILs
- Tumor biomarkers or prognostic factors (e.g. PD-L1, mesothelin, plasma osteopontin, etc.)
- Circulating (cytokines, chemokines, tumor biomarkers and antibody responses) including mesothelin, CEA, VEGF, and CA19-9
- Gene expression profiling of PBMCs and tumor tissue
- T cell receptor (TCR) profiling of PBMCs and tumors

Specific testing may include analysis for changes in protein analytes such as cytokines, antibodies, relevant tumor markers and markers of immune function by using enzyme-linked immunospot (ELISPOT), intracellular cytokine staining, enzyme-linked immunosorbent assay (ELISA), or other relevant methods including peptide or protein arrays. In addition, assays of immune cell phenotyping and functions or responses may be conducted using whole blood samples and PBMCs.

To explore whether a diverse T cell repertoire is predictive of response to therapy, sequencing of TCR genes may be performed on DNA isolated from peripheral blood and tumor to quantitate the composition of the T cell repertoire prior to and during therapy. Genetic markers associated with response or resistance may also be measured using peripheral blood DNA; peripheral blood DNA may also be used as a germline control to compare with tumor cell DNA. RNA isolated from peripheral blood for gene expression analysis may be used to characterize subjects who respond or are resistant to treatment. Additional assessments and methodologies may be used at the Sponsor's discretion.

6.4.4.4 Blood Cultures for CRS-207 Surveillance

Blood samples will be obtained from subject's peripheral vein at the EOT visit or 7 days after the last dose of CRS-207 (for patients continuing on pembrolizumab) (prior to initiation of antibiotics) to monitor for presence of CRS-207. For subjects with a central venous access device, 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 [redacted] and be re-tested until negative cultures are confirmed.

6.4.4.4.1 Confirmed Listeria Infection

In the event a subject has a positive Listeria culture at any time during or after study participation (except within 7 days after a CRS-207 infusion), Sponsor should be notified within 24 hours of the event (refer to Section 7.3.5).

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

6.4.4.4.2 Suspected Infection with CRS-207 or Listeria

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

If infection with CRS-207 is confirmed or suspected, IV antibiotics (Section 6.3.6) should be initiated as soon as possible and follow-up cultures obtained periodically to confirm absence/clearance of any CRS-207 infection. The Medical Monitor should be consulted regarding continuation of study drug treatment and treatment of suspected or confirmed infection.

6.4.5 Appropriateness of Measures

Tumor imaging is the gold standard for assessing monitoring disease progression and tumor response in patients with cancer. The primary efficacy variable, ORR, is generally an accepted surrogate of efficacy appropriate for use in single-arm studies with smaller sample sizes (Food and Drug Administration, 2007). Tumor response will be evaluated using both RECIST v1.1 and irRECIST. The inclusion of irRECIST accounts for the unique tumor response characteristics

reported for immune checkpoint inhibitors such as pembrolizumab (Nishino, 2013). Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. 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. Therefore, the standard RECIST v1.1 may not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab.

Additional secondary efficacy variables will also be derived from tumor imaging and response assessments. OS is the universally accepted direct measure of benefit and is an objective measure, although may be limited by difficulties with patient follow-up in smaller studies and confounded by non-cancer deaths in long-term studies.

Paired tumor biopsies and archival tissue will be analyzed for PD-L1 expression as well as other immune checkpoint molecules and infiltration of immune cells (e.g. T cell, myeloid and DC subpopulations) by IHC and gene expression profiling. PD-L1 expression may predict response to anti-PD-1 (Brahmer, 2010; Topalian, 2012). PD-L1 is also upregulated in response to IFN-γ released by infiltrating T cells and could potentially be a predictor of response to any active immunotherapy. Characterization of immune checkpoint expression as well as immune infiltrates may be predictive of response to therapy and may also give insight into next generation combinatorial approaches.

The safety parameters to be evaluated in this study include standard assessments such as recording of medical history, AEs and SAEs, physical examination, vital signs, ECGs, serum chemistry and hematology, urinalysis, concomitant medications, and other routine clinical and laboratory procedures.

6.5 Statistical Analysis

The completeness of the data affects the integrity and accuracy of the final study analysis. Therefore, efforts will be made to ensure complete, accurate and timely data collection, and to avoid missing data. The procedures for handling missing, unused, or spurious data, along with the detailed method for analysis of each variable, transformations, and exploratory analyses will be presented in the Statistical Analysis Plan (SAP); the information below is intended as a guide to planned analyses.

6.5.1 Sample Size Determination

This study is descriptive in nature, as such the sample size for this study is determined by practical rather than statistical considerations. Approximately 79 subjects will be enrolled to achieve at least 79 treated subjects with evaluable post-baseline tumor data. With 79 subjects, the precision for point estimate for ORR is as follows: the 95% confidence interval (CI) width for ORR based on Wilson score intervals are at most the observed proportion +/- 0.108. If the

observed ORR = 30.4% (24 of 79 subjects with PR or CR), the lower bound of the 95% CI would be 19.5%.

Of the 79 subjects enrolled, an estimated 50 subjects will be enrolled with gastric or GEJ cancer, and an estimated 29 subjects will be enrolled with esophageal cancer. Assuming at least 50 evaluable gastric/GEJ subjects are evaluable for ORR, the precision for point estimate for ORR is as follows: the 95% CI width for ORR based on Wilson score intervals are at most the observed proportion +/- 0.134. Assuming at least 29 evaluable esophageal cancer subjects are evaluable for ORR, the precision for point estimate for ORR is as follows: the 95% CI width for ORR based on Wilson score intervals are at most the observed proportion +/- 0.173.

6.5.2 General Considerations

The descriptive summary for the categorical variables will include counts and percentages. The descriptive summary for the continuous variables will include means, medians, standard deviations, Q1, Q3, and minimum and maximum values. The descriptive summaries of time to event data will include median, 25th and 75th percentiles, and standard error. All data will be listed for all subjects.

This study is descriptive in nature; no formal hypothesis testing will be performed. All CIs will be 95%, unless stated otherwise.

All statistical analyses will be performed using SAS.

The effects of noncompliance, dropouts, and covariates will be assessed to determine the impact on the general applicability of results from this study.

6.5.3 Subject Information

Subject disposition summaries will include the number of enrolled subjects, the number of subjects receiving study drug, the number of subjects completing the study, the number of subjects withdrawing prematurely, and the reasons for treatment and study discontinuation.

Demographics and baseline disease characteristics will be summarized using descriptive statistics.

6.5.4 Analysis Sets

Evaluable Analysis Set (EAS) is defined as all subjects who received at least 1 dose of CRS-207 and have at least one evaluable post-baseline RECIST tumor response assessment or were discontinued due to toxicity. The EAS will be the primary population for analyses of tumor-related endpoints (ORR, DCR, DOR, and PFS).

Full Analysis Set (FAS) is defined as all subjects who received at least 1 dose of CRS-207. The FAS will be used for analyses of OS, immunogenicity and other biomarker data, and sensitivity analysis of select tumor-related endpoints.

Safety Set (SAF) includes all subjects who received any study treatment (pembrolizumab or CRS-207). The SAF will be used for all analyses of safety data and may be used for select biomarker data.

Additional analysis sets (e.g. per protocol set) may be defined in the SAP.

6.5.5 Efficacy Analyses

All efficacy variables derived from tumor imaging and response assessments will be determined using RECIST v1.1 and irRECIST. The primary analyses of tumor related efficacy variables will be performed using objective disease responses definitions based on RECIST. Exploratory analyses will be performed separately using objective disease responses definitions based on irRECIST.

6.5.5.1 Primary Efficacy Variable and Analysis

The ORR is defined as the proportion of subjects with best overall response (BOR) of partial response (PR) or complete response (CR) according to RECIST v1.1. The proportion of subjects with ORR in the EAS, along with a 95% CI based on the Wilson Score interval, will be reported. Analyses of ORR described above may be repeated in FAS, treating missing BOR as a non-responder. Objective disease response at each visit and best overall response will also be summarized using the EAS.

6.5.5.2 Secondary Efficacy Variables and Analyses

Secondary efficacy variables in the study include:

Disease control rate (DCR) defined as the percentage of subjects with BOR of CR, PR, or SD. The analysis of DCR will be performed using the EAS and conducted in the same manner as ORR.

Progression-free survival (PFS) defined as time from first dose of study drug to first documentation of disease progression (per RECIST) or death due to any cause.

Subjects who do not experience disease progression and are alive on or before the data cut-off date will be censored at the time of last evaluable tumor assessment or data cut-off date, whichever is earlier. Subjects who do not experience disease progression and start new systemic anti-cancer therapy will be censored at the last evaluable tumor assessment on or prior to the time the new systemic anti-cancer therapy was begun or the data cut-off date, whichever is earlier. For analyses conducted in the FAS, subjects with no evaluable post-baseline tumor assessments will be censored at the time of receipt of first study drug. Subjects who are lost to follow-up for assessment of disease progression will be censored at their last evaluable tumor assessment or data cut-off date, whichever is earlier. The analysis of PFS will be performed in the EAS using Kaplan-Meier methods. Analyses may be repeated in the FAS.

Duration of response (DOR) includes subjects with an objective disease response (PR or CR) and is defined as the time from the first tumor assessment that supports the subject's objective

disease response to the time of disease progression or death due to any cause. Subjects who do not experience disease progression or death at the time of analysis will be censored using the same rules as described for PFS. The analysis of DOR will be performed in the EAS using Kaplan-Meier methods.

Overall Survival (OS) defined as the time from first dose of study drug 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, or the data cut-off date, whichever is earlier. OS will be performed in the FAS using Kaplan-Meier methods. The analysis may be repeated in the SAF.

6.5.5.3 Exploratory Variables and Analysis

Exploratory efficacy analyses will be evaluated based on the following variables:

- ORR, DCR, DOR and PFS using irRECIST (Nishino, 2013)
- Association of PD-L1 expression with clinical efficacy
- Association of mesothelin expression in tumor tissue with clinical efficacy

Additional efficacy analyses that may be evaluated include:

- Association of immunological responses with clinical efficacy
- Association with circulating and molecular biomarkers with clinical efficacy
- Impact of EBV status and other molecular characteristics including but not limited to human epidermal growth factor receptor 2 (HER2) status, MSI, and chromosomal instability (CIN), on clinical efficacy
- Association of molecular characteristics including but not limited to HER2 status and IFN-related gene signature with clinical efficacy

Exploratory analyses of the data will be conducted as deemed appropriate. Details of additional analysis of other variables are provided in the SAP.

6.5.6 Safety Analyses

AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1 or higher and assessed for severity using the NCI-CTCAE v. 4.03. The number and percentage of subjects experiencing any TEAE, overall, and by system organ class and preferred term will be tabulated. The incidence rates adjusted by cumulative exposure will also be presented overall and by cycle. AEs associated with clinical laboratory parameters will be characterized according to NCI CTCAE, Version 4.03. Shifts in toxicity grades from baseline to each visit will be summarized.

6.5.7 Research Laboratory Analyses

Analyses of research laboratory samples, tumor biopsies, and immune response data will be described separately outside the context of the SAP.

6.5.8 Timing of Analysis

The final analysis will be performed after all subjects have completed at least 6 cycles of treatment or discontinued study treatment and completed the EOT Visit. A supplemental analysis may be completed at the end of study that includes the cumulative data collected after the final analysis (i.e. through the Follow-up Period).

6.5.9 Data Monitoring Committee

There will be no formal Data Monitoring Committee for this study. Safety data and all unacceptable toxicities will be reviewed by the SRT comprised of participating investigators in the study, the Medical Monitor, and representatives of the Sponsor.

7 ADVERSE EVENT REPORTING AND FOLLOW UP

7.1 Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE 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. All AEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

AEs occurring from the time of first study drug administration and up to 28 days after the last dose of study drug or until a subject initiates a new cancer therapy, whichever is earlier, will be monitored and documented on the AE eCRF. AEs include clinical laboratory test variables and events observed by the Investigator; subjects should be instructed to report any AE that they experience to the Investigator. At each indicated visit, Investigators should make an assessment for AEs and record the event on the appropriate AE 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 AE 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 AE, not the procedure.

Any medical condition already present prior to the first dose of study drug should be reported in medical history 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 AE.

Clinically significant abnormal laboratory or other examination (e.g. ECG) findings that are detected during the study or are present at screening and significantly worsen during the study should be reported as AEs. 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 AE.

Examples of AEs include the following:

- Significant or unexpected worsening or exacerbation of the indication under study
- Exacerbation of a chronic or intermittent preexisting condition, including an increase in frequency or intensity of the condition

- New conditions detected or diagnosed after investigational agent administration even if they were present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction with another medical product
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational agent or a concurrent medication.

An overdose should not be reported as an AE or SAE; instead, the symptoms resulting from the overdose should be reported as the AE or SAE.

Examples of AEs do not include the following:

- Medical or surgical procedures (e.g. endoscopy, appendectomy); instead, the medical condition that led to the procedure is an AE
- Situations that are unwanted but in which an untoward medical occurrence did not occur (e.g. social inconvenience after admission to a hospital)
- Anticipated day-to-day fluctuations of a pre-existing disease or condition (present or detected before enrollment) that does not worsen overall

A follow-up is required for all subjects with AEs until the event has been resolved or the condition has stabilized. In case of unresolved AEs, including significant abnormal laboratory values at the EOT visit assessment, these events will be followed up until resolution or until they become clinically not relevant.

7.1.1 Disease Progression and Other Events of Clinical Interest

7.1.1.1 Disease Progression

Progression of the cancer under study is not considered an AE in this study unless it is considered to be drug-related by the investigator. The term "disease progression" should be recorded as an AE/SAE only if there are no other identifiable AEs/SAEs associated with the disease progression at the time of reporting. For events associated with disease progression, the relevant signs and symptoms should be reported using a diagnosis whenever possible rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE. If the events resulting from disease progression meet the criteria for an SAE (e.g. resulted in hospitalization, a life-threatening event, or death), the specific event(s) should be reported as an SAE(s). In both cases (i.e. AEs or SAEs related to disease progression), it should be indicated that each event (reported as a diagnosis or as signs and symptoms) is related to disease progression on the AE eCRF.

7.1.1.2 Events of Clinical Interest

[redacted]

Drug-Induced Liver Injury

Serum chemistry laboratory values consistent with Hy's Law criteria (i.e. all 3 of the following must coexist):

- ALT or AST ≥ 3 × ULN
- Total bilirubin ≥ 2 × ULN
- ALP < 2 × ULN

Laboratory values meeting all criteria for potential Hy's Law cases from the time of first study drug administration through the EOT visit are considered ECI and should be reported following SAE reporting procedures (Section 7.3).

7.1.2 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each AE and the potential relationship between the AE and the study medication.

Assessment of Severity:

The severity of all AEs should be graded according to the NCI-CTCAE v. 4.03 (http://ctep.cancer.gov/reporting/ctc.html). For AEs not listed in the CTCAE, the following grading system should be used:

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

Attribution:

The Investigator is obligated to estimate the relationship between the investigational agents and the occurrence of each AE or SAE using 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 agents should be considered and investigated. The Investigator should 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 AE and render a causality assessment based on the most likely contributing factor to the AE.

There may be situations when an SAE has occurred and the Investigator has minimal information to include in the initial report. However, the Investigator must 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 assessment of the relationship between the AE and the study medication will be determined using one of the following attribution categories as outlined in the NCI Guidelines: Adverse Event Reporting Requirements (2013).

RELATIONSHIP	**ATTRIBUTION**	**DESCRIPTION**
Unrelated to investigational agent/intervention	Unrelated	The AE *is clearly NOT related* to the intervention
	Unlikely Related	The AE *is doubtfully related* to the intervention
Related to investigational agent/intervention	Possibly Related	The AE *may be related* to the intervention
	Probably Related	The AE *is likely related* to the intervention
	Definitely Related	The AE *is clearly related* to the intervention

AEs listed as possibly, probably, or definitely related are considered to have a suspected “reasonable causal relationship” to the investigational agent/intervention (ICH E2A). The expression "reasonable causal relationship" is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship

7.2 Serious Adverse Events

An AE 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 AE
  - NOTE: An AE 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 1 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 AEs 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) or for observation post-study drug administration will not be considered a SAE.
- 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.

7.3 Serious Adverse Event Reporting − Procedures for Investigators

7.3.1 Initial Reports

SAEs will be collected from the time of first study drug administration through 90 days following cessation of treatment, or 28 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. SAEs and events of clinical interest must be reported to the Sponsor (or designee) within 24 hours of the knowledge of the occurrence. Outside of the 90-day period, only SAEs considered related to the administration of study drug must be reported to the Sponsor.

In the event an SAE is observed or reported, the SAE report will be completed as thoroughly as possible including all available details about the event and the signature of the Investigator. If the Investigator does not have all information about an SAE, the Investigator will not wait to receive additional information before notifying the Sponsor of the event and completing the form. The form will be updated when additional information is received.

Complete the paper SAE form for each SAE. The SAE form will be faxed or emailed to the Sponsor or designee within 24 hours of awareness of the initial or any follow-up information, and designated study personnel will be notified electronically. If the SAE falls on a weekend or

holiday, an email notification is acceptable but must be followed by an SAE reporting form on the next business day.

7.3.2 Safety Reporting Contact Information

Safety contact information may be found in the Study Reference Manual.

7.3.3 Expedited Reporting Requirements

The Sponsor (or designee) will report all SAEs that are unexpected and considered related to the administration of the investigational agent to the appropriate health and regulatory authorities and Investigators in the form of an expedited safety report within 15 calendar days after receiving information on the SAE. The Investigators will notify their reviewing IRB/EC and other committee(s) as required by institutional policies.

The Sponsor will also report to the appropriate health and regulatory authorities by facsimile, e-mail, or phone within 7 days of receiving the information, any unexpected life-threatening or fatal SAEs that are considered related to the investigational agent.

7.3.4 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 and submit any supporting documentation (e.g. subject discharge summary or autopsy reports) via fax or e-mail to the Sponsor or designee.

7.3.5 Adverse Events of Special Interest

Suspected infection with CRS-207 and/or *Listeria* are considered AESIs and should be reported following SAE reporting procedures in Section 7.3 irrespective of temporal relationship to study drug administration.

In the event a subject has a positive *Listeria* culture at any time during or after study participation (except within 4 days after a CRS-207 infusion), a detailed narrative of the event should be reported to the Sponsor within 24 hours of the event.

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

7.4 Pregnancy Reporting

If the subject or partner of a subject participating in the study becomes pregnant during the study or within 120 days of discontinuing study drug (or 28 days if the subject initiates new anticancer therapy, whichever is earlier) the Investigator should report the pregnancy within 24 hours of being notified. Designated safety personnel 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 EOT study procedures will be performed.

The subject or partner 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 designated safety personnel. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. SAE reporting procedures should be followed if the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e. postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly).

8 DATA MANAGEMENT AND RECORD KEEPING

8.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed by the clinical research associate (CRA) during monitoring visits. The CRA will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data has been accounted for and electronically signed by the Investigator or assignee.

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

8.2 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.

8.3 Medical Information Coding

For medical information, the following thesauri will be used:

- Latest version of MedDRA (version 18.1 or higher) for medical history and AEs, and
- World Health Organization Drug Dictionary Enhanced (Sept. 2015 or later) for prior and concomitant medications.

8.4 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the 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 site for resolution through data queries.

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

8.5 Record Keeping

Records of subjects, source documents, monitoring visit logs, eCRFs, inventory of study drugs, 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 Study 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.

9 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

9.1 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.

9.2 Investigator Requirements

Each Investigator must provide the Sponsor and/or its designee a completed and signed Form FDA 1572 and a Financial Disclosure Form. All sub-Investigators must be listed on Form FDA 1572 and Financial Disclosure Forms must be completed for all sub-Investigators listed on Form FDA 1572.

A Coordinating Investigator will be identified for multicenter trials conducted in the EU and Australia. The Coordinating Investigator will be selected on the basis of active participation in the trial, thorough knowledge of the therapeutic area being studied, and the ability to interpret data.

9.2.1 Disposition and Accountability of Investigational Products

The Investigator is responsible for the control of investigational products under study. An investigational product dispensing log must be kept current and should contain the following information:

- The identification number for each subject who is administered the investigational product
- The date(s) and quantity of the investigational product administered to the subject
- Documentation of proper disposal of used investigational product vials or unused vials subjected to temperature excursion
- Documentation of proper disposal (or return, at Sponsor's request) of unused investigational product vials.

The Investigator is responsible for investigational product accountability during on-site monitoring visits. All records and used/unused supplies of the investigational product must be available for inspection at every monitoring visit.

The study sites, per institutional guidelines, will destroy used investigational product vials after formulation for administration. The formulation of investigational product for administration and the destruction of each used vial will be documented in the investigational product accountability log. Unused investigational product will be destroyed at the study site after final investigational product accountability and notification by Sponsor, unless otherwise directed by Sponsor.

9.3 Institutional Review Board/Ethics Committee

The IRB/EC 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/EC 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/EC by the Investigator.

Federal regulations and International Conference on Harmonisation (ICH) require that approval be obtained from an IRB/EC 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/EC.

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

9.4 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/EC prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

The Investigator must ensure each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure 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 will document consent was obtained prior to enrollment in the study in the source documentation. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, auditors, the IRB/EC, and/or regulatory agencies. A copy of the signed ICF will be given to the subject.

9.5 Study Monitoring Requirements

To ensure the study is conducted in accordance with the protocol and ICH GCP, the study monitor will 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 management, 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 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 are entered by the site, the monitor 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 site by signature and date on the study-specific monitoring log.

9.6 Disclosure of Data

Data generated by this study must be available for inspection by health and regulatory authorities (such as FDA, Health Canada, European Medicines Authority, and others), the Sponsor or designee, and the IRB/EC 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.

9.7 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, e.g. 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.

9.8 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.

9.9 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.

9.10 Insurance and Indemnity

In accordance with the relevant national regulations, the Sponsor has taken out subject liability insurance for all subjects who have given their consent to the clinical study. This cover is designed for the event that a fatality, physical injury, or damage to health occurs during the clinical study's execution.

9.11 Legal Aspects

The clinical study is submitted to the relevant national competent authorities in all participating countries to achieve a clinical trial authorization (CTA).

The study will commence (i.e. initiation of study centers) when the CTA and favorable ethics opinion have been received.

10 REFERENCES

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11 IMMUNE-RELATED RESPONSE CRITERIA IN SOLID TUMORS

Based on an analysis of patients with melanoma enrolled in pembrolizumab study KEYNOTE-001, 7% of evaluable subjects experienced delayed or early tumor pseudoprogression. Of note, patients who had progressive disease by RECIST v1.1 but not by immune-related response criteria had longer OS than patients with progressive disease by both criteria. Additionally, the data suggest that RECIST v1.1 may underestimate the benefit of pembrolizumab in approximately 15% of patients. These findings support the need to apply a modification to RECIST v1.1 that takes into account the unique patterns of atypical response in immunotherapy and enable treatment beyond initial radiographic progression.

Immune-related RECIST (irRECIST) is RECIST v1.1 adapted to account for the unique tumor response seen with immuno-therapeutics as described in Nishino et al. 2013 (Nishino, 2013). The assessment of unidimensional target lesions and response categories per irRECIST are identical to RECIST v1.1. However, Merck has implemented an adaptation related to new lesions, non-target and tumor burden assessment in order to confirm radiographic progression. irRECIST will be used by local site investigators to assess tumor response and progression, and make treatment decisions in support of ORR endpoint.

Therefore, RECIST v1.1 will be used with the following adaptations:

In subjects who have initial evidence of radiological progressive disease (PD) by RECIST v1.1 as determined by the site, it is at the discretion of the PI whether to continue a subject on study treatment until repeat imaging is obtained (irRECIST subject management). This clinical judgment decision by the site should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive study treatment and tumor assessment should be repeated ≥ 4 weeks later in order to confirm PD by irRECIST per site assessment. Clinical stability is defined as the following:

1. Absence of symptoms and signs indicating clinically significant progression of disease, including worsening of laboratory values
2. No decline in ECOG performance status
3. Absence of rapid progression of disease
4. Absence of progressive tumor at critical anatomical sites (e.g. cord compression) requiring urgent alternative medical intervention

In determining whether or not the tumor burden has increased or decreased per irRECIST, the local site investigator should consider all target and non-target lesions as well as any incremental new lesion(s).

Scenarios where PD is confirmed at repeat imaging if ANY of the following occur by irRECIST:

- Tumor burden remains ≥ 20% and at least 5 mm absolute increase compared to nadir
- Non-target disease resulting in initial PD is qualitatively worse

- New lesion resulting in initial PD is qualitatively worse
- Additional new lesion(s) since last evaluation
- Additional new non-target progression since last evaluation

If repeat imaging confirms PD due to any of the scenarios listed above, subjects will be discontinued from study therapy (exception noted below).

Scenarios where PD is not confirmed at repeat imaging if ALL of the following occur by irRECIST:

- Tumor burden is < 20 % or < 5 mm absolute increase compared to nadir
- Non-target disease resulting in initial PD is qualitatively stable or improved
- New lesion resulting in initial PD is qualitatively stable or improved
- No incremental new lesion(s) since last evaluation
- No incremental new non-target progression since last evaluation

If repeat imaging does not confirm PD by irRECIST and the subject continues to be clinically stable, treatment may continue and follow the regular imaging schedule. When feasible, subjects should not be discontinued until progression is confirmed by the local site investigator/radiology assessment. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. Subjects that are deemed clinically unstable are not required to have repeat tumor imaging for confirmation of PD. Tumor flare includes any of the following scenarios:

- Worsening of existing target lesion(s)
- Worsening of existing non-target lesion(s)
- Development of new lesion(s)

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen with treatment of pembrolizumab. Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. 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 1.1 may, thus, not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab.

irRECIST is RECIST v1.1 adapted to account for the unique tumor response seen with immuno-therapeutics as described in Nishino et al. 2013 (Nishino, 2013). The assessment of unidimensional target lesions and response categories per irRECIST are identical to RECIST v1.1. However, Merck has implemented an adaptation related to new lesions, non-target and tumor burden assessment in order to confirm radiographic progression. irRECIST will be used

by local site investigators to assess tumor response and progression, and make treatment decisions.

Therefore, RECIST v1.1 will be used with the following adaptations:

In subjects who have initial evidence of radiological PD by RECIST v1.1 as determined by the site, it is at the discretion of the PI whether to continue a subject on study treatment until repeat imaging is obtained (irRECIST subject management). This clinical judgment decision by the site should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive study treatment and tumor assessment should be repeated ≥ 4 weeks later in order to confirm PD by irRECIST per site assessment. Clinical stability is defined as the following:

1) Absence of symptoms and signs indicating clinically significant progression of disease, including worsening of laboratory values

2) No decline in ECOG performance status

3) Absence of rapid progression of disease

4) Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention

In determining whether or not the tumor burden has increased or decreased per irRECIST, the local site investigator should consider all target and non-target lesions as well as any incremental new lesion(s).

Scenarios where PD is confirmed at repeat imaging if ANY of the following occur by irRECIST:

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

If repeat imaging confirms PD due to any of the scenarios listed above, subjects will be discontinued from study therapy (exception noted below and in Section 6.4.2.1).

Scenarios where PD is not confirmed at repeat imaging if ALL of the following occur by irRECIST:

- Tumor burden is < 20 % or < 5 mm absolute increase compared to nadir
- Non-target disease resulting in initial PD is qualitatively stable or improved
- New lesion resulting in initial PD is qualitatively stable or improved

- No incremental new lesion(s) since last evaluation
- No incremental new non-target progression since last evaluation

If repeat imaging does not confirm PD by irRECIST and the subject continues to be clinically stable, treatment may continue and follow the regular imaging schedule.

When feasible, subjects should not be discontinued until progression is confirmed by the local site investigator/radiology assessment. This allowance to continue treatment despite initial radiologic progressive disease (PD) takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. Subjects that are deemed clinically unstable are not required to have repeat tumor imaging for confirmation of PD. Tumor flare includes any of the following scenarios:

- Worsening of existing target lesion(s)
- Worsening of existing non-target lesion(s)
- Development of new lesion(s)

SIGNATURE PAGE

STUDY TITLE: A Phase 2, Open-label Evaluation of CRS-207 and Pembrolizumab in Adults with Recurrent or Metastatic Gastric/Gastroesophageal Junction or Esophageal Adenocarcinomas

I, the undersigned, have read Protocol ADU-CL-14 and agree it contains all necessary information required to conduct the study.

Signature	Date
Natalie Sacks	22 Aug 17

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

INVESTIGATOR AGREEMENT

STUDY TITLE: A Phase 2, Open-label Evaluation of CRS-207 and Pembrolizumab in Adults with Recurrent or Metastatic Gastric/Gastroesophageal Junction or Esophageal Adenocarcinomas

By signing below I agree that:

I have read the protocol and agree it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provisions 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 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 this information is confidential and proprietary to Aduro Biotech and 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, 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 United States Food and Drug Administration Regulations, Institutional Review Board/Ethics Committee Regulations, and International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name