A PHASE 2, OPEN-LABEL EVALUATION OF CRS-207 AND PEMBROLIZUMAB IN ADULTS WITH RECURRENT OR METASTATIC GASTRIC, GASTROESOPHAGEAL JUNCTION, OR ESOPHAGEAL ADENOCARCINOMAS

Abbreviated Statistical Analysis Plan

VERSION 1.0
DATE OF PLAN:

13Mar2018

STUDY DRUG:
CRS-207

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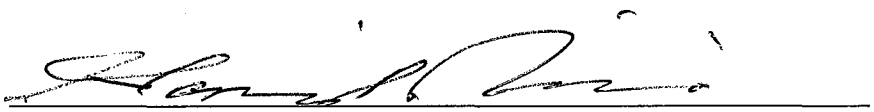

13Mar2018

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Date

Contents

ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase
ASAP	Abbreviated statistical analysis plan
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Class
BUN	Blood Urea Nitrogen
CTCAE	Common Terminology Criteria for Adverse Events
CFU	Colony-forming units
CI	Confidence Interval
CSR	Clinical study report
DCR	Disease Control Rate
DOR	Duration of Response
ECG	Electrocardiogram
EOT	End of treatment
GEJ	Gastroesophageal Junction
IRR	Infusion-Related Reactions
irRECIST	Immune-response RECIST
MedDRA	Medical Dictionary for Medical Affairs
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression Free Survival
PR	Partial Response
PT	Preferred Term
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SD	Stable Disease
SI	International System of Units
SOC	System Organ Class
SRT	Safety Review Team
TEAE	Treatment-Emergent Adverse Event
WBC	White Blood Cell
WHO	World Health Organization

1. INTRODUCTION

This is an abbreviated statistical analysis plan (ASAP) designed to outline the planned analysis required to satisfy the Clinical Study Report (CSR) synopsis of study number ADU-CL-14: A Phase 2, Open-label Evaluation of CRS-207 and Pembrolizumab in Adults with Recurrent or Metastatic Gastric, Gastroesophageal Junction, or Esophageal Adenocarcinomas. The derivation and analysis of selected immunological/tumor marker endpoints, if performed, will be discussed in another standalone document. The statistical analyses and summary tabulations described in this ASAP will provide the basis for the CSR synopsis reporting of the final analysis results from this trial. Population, data handling rules, statistical methods, changes from the study protocol, and formats for data presentation are provided. Content of this SAP is based on the protocol version Amendment 2. Protocol revision history appears as follows:

Original	20 December 2016
Amendment 1	17 July 2017
Amendment 2	22 August 2017

2. STUDY OBJECTIVES AND ENDPOINTS

Objectives	**Variables**
Assess safety and tolerability of CRS-207 and pembrolizumab	Safety will be assessed based on adverse events (AEs) and changes in: clinical laboratory assessments; ECOG performance status; vital signs; weight; physical examination; electrocardiogram (ECG) parameters; and concomitant medications. Blood will also be tested for CRS-207 clearance.
Evaluate the effect of CRS-207 and pembrolizumab on tumor response and survival	Tumor measurements will be performed by radiologic evaluation (CT). All tumor response variables will be assessed by the Investigator using RECIST v1.1 and irRECIST. <u>Primary Efficacy Variable:</u> • Objective response rate (ORR), defined as the proportion of subjects with complete response (CR) or partial response (PR) according to RECIST v1.1 <u>Secondary Efficacy Variables:</u> • Disease control rate (DCR), defined as the percentage of subjects with CR, PR, or stable disease (SD) • Progression free survival (PFS) defined as time from first dose of study drug until disease progression or death • Duration of response (DOR) defined as the time from first PR or CR until PD or

Objectives	Variables
	death. DOR 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. • Overall survival (OS), as measured from date of first dose of study drug until death <u>Exploratory Efficacy Variables:</u> • ORR, DCR, DOR and PFS using irRECIST
Characterize the immune response, [redacted], and molecular characteristics of the tumor microenvironment following administration of CRS-207 and pembrolizumab	This ASAP will not include this objective. If performed, the analysis will be discussed in another standalone document.

This ASAP provides derivation and listing of OS, PFS, DOR and tumor response assessment. No summary tables will be produced for these endpoints.

3. STUDY DESIGN

3.1. Study Design and Population

ADU-CL-14 is an open-label, single-arm, multicenter clinical study in approximately 79 adults with recurrent or metastatic gastric, gastroesophageal junction (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. 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 [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 7 days after the last CRS-207 dose [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. 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, 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.

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. 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. 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 the protocol. 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.

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*, 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.

3.2. Randomization and Blinding

ADU-CL-14 is a single-arm, open-label study. Since all subjects will receive the same investigational products, randomization and blinding are unnecessary; study drug will be provided open-label.

3.3. Sample Size Considerations

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.

3.4. Interim Analysis

A Safety Review Team will monitor data during the study, as described in Section 3.1. Otherwise, no other formal interim analysis activities are planned per the protocol.

3.5. Timing of Analyses

On 12 December 2017, Aduro decided to cease development activities of CRS-207 and close out ongoing studies. As of 31 January 2018 every subject had completed their end of treatment visit. No additional follow-up of these subjects is expected. This ASAP details the analysis plans for the CSR synopsis as of the final database lock.

4. DATA ANALYSIS CONSIDERATIONS

All analyses will be conducted based on SAS 9.3 or higher.

All data in the database will be presented in by-subject data listings.

Unless otherwise stated, all listings will be sorted by site ID, subject number, and assessment date (and time, if available).

Unless stated otherwise, continuous data will be summarized based on n, mean, median, standard deviation (SD), first quartile (Q1), third quartile (Q3), minimum value, and maximum value. For continuous variables, if n=1, the SD cannot be calculated and will be displayed as (NA).

Unless stated otherwise, categorical data will be summarized using n and percentage based on the number of nonmissing values.

- The number of missing values will be presented as a separate category with no percentage, but only if one or more subjects are missing data.
- Counts of zero will be presented without percentages.

Precision

- Mean, Median, Q1, and Q3: one additional decimal place to that reported for Minimum and Maximum
- SD: two additional decimal places than the Minimum and Maximum
- Percentages: reported to one decimal place

No statistical significance test will be performed.

With exception to missing data handling noted in section 5.6, data will not be imputed for analysis purposes.

Summaries by visit will be produced for sample sizes ≥ 2.

Numbering for data displays will be based on ICH E3.

4.1. Stratification and Covariates

There are no formal plans for analysis stratification.

4.2. Evaluation of Subgroups

Subgroup analyses are not planned to be performed for the final analysis.

4.3. Multiple Comparisons and Multiplicity

Not Applicable.

5. GENERAL DATA HANDLING CONVENTIONS

5.1. Assigned and Actual Treatment

All subjects enrolled in the study are assigned to combination therapy.

5.2. Reference Dates

- Age and time from diagnosis of disease will use the enrollment date as their reference date.
- Safety data, such as AEs and laboratory assessments will use the first date of study treatment as a reference date.
- Efficacy data will use the first date of study treatment as a reference date.
- Study Day will use the first date of study treatment.

5.3. Study Day and Duration Variables

Reference date calculations will be defined as the following:

- date of interest – reference date + 1 when the date of interest >= reference date;
- otherwise, date of interest – reference date.

For instance, study day will be based on the date of first study treatment as the reference would either have a negative value if collected before dosing or a positive value if collected after drug dosing; there will be no study day zero.

Duration of time is dependent on reference dates and will be calculated in a manner similar to that of the reference date calculation, assuming that dates of interest will strictly follow reference dates (e.g. no negative values). For example, duration on study is defined as the end of study date – enrollment date + 1. Duration of treatment is defined as the last date of treatment – first dose date + 1. Duration of the safety observation period is defined as (the last date of treatment

+ 28 days) – first dose date + 1. Subjects still receiving ongoing treatment or participating in study follow up at the time of analysis will use imputed treatment end and end of study dates as described in section 5.6.

Survival, or time-to-event, endpoints such as PFS or OS are followed until first event or censoring. As a result, survival time will be calculated as: event or censoring date – reference date + 1. These are further described in Section 7.

When reporting survival or duration outcomes, the results (in days) above will be converted to an appropriate unit. When reporting in months it will be divided by 30.4375; for reporting in weeks it will be divided by 7; and for reporting in years it will be divided by 365.25.

5.4. Study Time Periods

Safety reporting will be classified by the following study periods for analysis:

Pre-therapy is defined as the period prior to a subject's first dose of study treatment.

On-therapy is defined as the period between first dose of study treatment and within 28 days following the last dose of study treatment.

Post-therapy is defined as the period of time following the on-therapy period.

5.5. Baseline, Post-Baseline Changes, and Endpoint

Baseline will be based on the last nonmissing value collected prior to or on the date [and time, if applicable] of first study treatment. Post-baseline values will be those collected after first dose of study drug.

Change from baseline is defined as: value – baseline value.

Percentage change from baseline is defined as: (value – baseline value)/baseline value X 100%.

Most extreme change: The maximum most extreme change will be the maximum post-baseline value; the minimum most extreme change will be the smallest post-baseline value. This calculation will consider all assessments collected within the on-therapy period, scheduled or unscheduled.

5.6. Imputation of Partial Dates

Adverse Events and Concomitant Medications

- If the AE start date is completely missing, no imputation will be conducted.
- If the AE start date is missing day and month, do the following:
    - If the treatment start date is missing or the AE year does not fall in the same as that of first treatment or if the AE contains information to indicate that the event

ended before the date of first study treatment (e.g. AE end date month and year are earlier than the treatment start date or the full date is known and occurs earlier than the date of first treatment), then set the start month and day to January 1st
    - Otherwise, set the start date to the date of first study treatment
- If only the day is missing, do the following:
    - If the study treatment start date is missing or the month and year does not fall in the same as that of first treatment or if the AE contains information to indicate that the event ended before the date of first study treatment, then set the start month and day to the 1st of the stated month
    - Otherwise, set the start date to the date of first study treatment
- End dates will not be imputed

Subsequent Anticancer Therapy, Radiotherapy or Anticancer Surgical Procedures

Partial dates for subsequent therapies will not typically be imputed, but may be needed to support efficacy outcome derivation for oncology studies. This typically applies to anti-cancer therapy and radiotherapy, but may also apply to surgical procedures. In this case, the following will be applied for imputation of new anti-cancer therapies taken after first study treatment:

- If the start date is completely missing, no imputation will be conducted
- If the start date is missing day and month, do the following:
    - If progressive disease (PD) has been identified in the year noted, new anti-cancer therapy date will be assigned to begin one day after the date of PD.
    - Otherwise the new anti-cancer therapy date will be assigned to January 1st.
- If only the day is missing, do the following:
    - If PD has been identified in the year noted, new anti-cancer therapy date will be assigned to begin one day after the date of PD.
    - Otherwise the new anti-cancer therapy date will be assigned to the 1st of the stated month.

Overall Response Date

For each visit-specific disease assessment, the date of overall response will need to be established. For CR and PR, set the date of overall response to the latest of all tumor assessments for the specified visit. Otherwise, set to the earliest date of all assessments made during the specified visit.

Treatment End Date

Missing treatment end dates will not be imputed at the end of the study. However, due to ongoing reporting needs, treatment end date will be imputed as the earliest of the data cutoff date, date of death, or date of study treatment withdrawal.

End of Study Date

Missing study end dates will not be imputed at the end of the study. However, due to ongoing reporting needs, end of study dates will be imputed as the earliest of the data cutoff date or date of death.

5.7. Lost to Follow Up or Lapse of Adequate Assessments

If a subject has missed two or more scheduled disease assessments, a censoring date will be required in support of relevant efficacy survival derivations. For example, PFS will be censored at the last adequate disease assessment prior to the lost to follow up window. However, this survival outcome would be considered censored after an extended amount of time without additional assessment (after two have been missed). Based on a protocol specified disease assessment schedule of every other cycle (every 8 weeks, up to 7 days prior to dosing), a lapse window of 112 days would be used to establish a censoring date.

6. STUDY SUBJECT DATA

6.1. Analysis Sets

The Safety Analysis Set (SAF) includes all subjects who received any study treatment. All analyses of safety data will be conducted using the safety set. The SAF is the only analysis set used for all listings and analysis.

6.2. Subject Disposition

Summaries of analysis population membership; final study status (ongoing or discontinuation), including reasons for study discontinuation; treatment status (ongoing or discontinued), including reasons for treatment discontinuation will be produced based on all subjects enrolled in the study. Time on study and duration of treatment will also be summarized.

Screen failures and final subject disposition status will be listed.

6.3. Protocol Deviations

Protocol deviations will be identified and classified as major (violations) before the database is locked. Major protocol deviations may include but are not limited to:

- Violation of Inclusion/Exclusion Criteria
- Dose not properly administered, including
    - Administrations in which protocol required pre-medication were not administered
- Use of prohibited medications

A listing of all protocol deviations will not be provided as part of the study report.

6.4. Demographic and Baseline Characteristics

Subject demographics will be summarized and listed for the SAF. These will include age, sex (Male / Female), ethnicity (Hispanic or Latino / Not Hispanic or Latino), race (American Indian or Alaska Native / Asian / Black or African American / Native Hawaiian or Pacific Islander / White/ Other), baseline height (cm), baseline weight (kg), baseline BMI (kg/m^2), and baseline BSA (m^2). Age will also be categorized as a categorical variable (< 65, ≥ 65) for reporting.

The following conversions and equations will be used as applicable:

- Height (in cm) = height (in inches) * 2.54
- Weight (in kg) = weight (in lbs) * 0.4536
- BMI (kg/m^2) = weight(kg)/[height$(m)^2$]
- BSA(m^2) = $\sqrt{}$[(height(cm)*weight(kg))/3600]

Duration of time from initial diagnosis to enrollment (in months); cancer type; Siewert classification (where applicable); TNM staging at diagnosis; TNM staging at enrollment; stage at study entry; tumor grade at diagnosis; tumor grade at enrollment; prior systemic therapy, prior radiation and prior surgery (Yes/No); and baseline ECOG will be summarized.

6.5. Medical History

Medical history will be listed.

6.6. Prior and Concomitant Medication

Concomitant medications will be coded to ATC and preferred name based on the WHO Drug Dictionary (WHO-DDE B2, March 2017). Prior medications are those which have been identified to have been discontinued prior to first study treatment (e.g. taken exclusively during the pre-therapy period). Concomitant medications are those which have been identified to have been taken at any point during the on-therapy period.

Prior and concomitant medications will be presented in data listings; medications which do not occur during the on-therapy period will be identified.

Concomitant implants, defined as all implants reported in the eCRF, will be presented in a data listing.

6.7. Anticancer Therapies

Anticancer therapies will be coded to ATC and preferred name based on the WHO Drug Dictionary (WHO-DDE B2, March 2017) and presented in a data listing.

Prior cancer related surgeries and systemic therapies, as well as prior radiotherapy, will be listed.

6.8. Study Drug Exposure

Duration of treatment (in months, as described in 5.3) will be summarized as a continuous variable for CRS-207 and pembrolizumab separately.

The number of infusions of CRS-207 will also be reported as both a continuous and categorical outcome; categories for reporting will be < 5 infusions; 5 to 10 infusions; > 10 to 15 infusions; and > 15 infusions.

The number of cycles of administration (of any dose amount) of pembrolizumab will be reported as a continuous and categorical outcome; categories for reporting will include: < 5 Cycles; 5 to 15 Cycles; > 15 to 25 Cycles; and > 25 Cycles.

The average volume administered for each infusion (or cycle) will be summarized by therapy. This will be calculated for each subject in (mL / infusion or mL / Cycle):
(Sum of Total Volume Administered [mL]) / (Total Number of Administrations)

The average dose intensity for each pembrolizumab cycle will be summarized. This will be calculated for each subject in (mg / Cycle):
(Sum of Total Dose Received [mg]) / (Total Number of Administrations)

The incidence of infusion interruptions and dose reductions, as well as the total number of interruptions and dose reductions, will be displayed by therapy. Reasons for infusion interruptions will be summarized by therapy.

The exposure summary display will be based on the Safety Set.

CRS-207 and pembrolizumab administration, infusion interruption, and dose reduction information, as well as derived drug exposure metrics, will be listed.

7. EFFICACY

All efficacy endpoints will listed but not summarized.

7.1. Primary Efficacy Endpoint

The primary efficacy endpoint and efficacy endpoints will be derived and listed but not summarized.

Objective Response Rate

A subject's BOR is determined by the highest qualitative value assessed during the study given a hierarchy of overall response results: CR > PR > SD > PD > NE. Response will be defined according to RECIST v1.1. In order for a valid value of SD to be assigned, there must be evidence of stable disease for at least 6 weeks. If the minimum time for SD has not been met on the first assessment, the assignment of BOR will depend on subsequent response assessments.

Subjects which do not have follow up data after a first assessment of SD prior to the minimum time requirement will be considered as not evaluable. BOR will be based on assessments collected after the first dose of study until disease progression; assessments collected after the start of new cancer treatment will not be considered.

Objective response is achieved for subjects who have a BOR of CR or PR according to RECIST v1.1. ORR is defined as the number of subjects who exhibit a BOR response of CR or PR divided by the number of subjects evaluable for analysis and will not be summarized or reported in the CSR synopsis.

7.2. Secondary Efficacy Endpoints

Disease Control Rate

Disease control is achieved by subjects who exhibit a BOR of CR, PR, or SD according to RECIST v1.1. DCR is defined as the number of subjects who exhibit a BOR response of CR, PR, or SD divided by the number of subjects evaluable for analysis and will not be summarized or reported in the CSR synopsis.

Progression Free Survival

PFS is defined as the number of weeks from the date of first dose of study treatment to the first date of objectively determined progressive disease according to RECIST v1.1 or death from any cause and is computed as described in Section 5.3. The primary analysis of PFS will include tumor assessments collected after the end of study treatment. Tumor assessments taken after switch to another anti-cancer therapy will be excluded from consideration.

The first date of objectively determined progressive disease would be the earliest date of any post-baseline overall response finding of progressive disease as part of the tumor lesion assessment data or death, unless a subject is censored at an earlier date. If an assessment occurs over several days, the method described in Section 5.6 will be used. If there are no adequate assessments for a subject, they will be censored on their first dose date unless they died prior to having their first assessment (in which case they will be considered to have had a PFS event of death). If a subject receives subsequent anticancer therapy prior to documentation of progressive disease, PFS will be censored at the latest adequate assessment prior to therapy initiation.

Subjects who progress or die following an extended period of follow up will also be censored at a latest adequate assessment prior to the end of a predefined lapse window, even if information is available regarding progression or death after this extended period. Should a subject die after the end of this lapse window they will be censored at their first dose date. The lapse window after which PFS events will not be considered is defined in Section 5.7.

Otherwise, if a subject does not have documented progression, the subject will be censored at the latest adequate assessment.

PFS will be listed.

Overall Survival

OS is defined as the number of weeks from the date of first dose of study treatment to the date of death from any cause and is computed as described in Section 5.3. Subjects still alive as of the data cut-off date will be censored on the last known alive date from mortality status follow up. For subjects that are lost to follow up, the last visit in the database or last contact date where the subject is documented to be alive will be used to estimate last known date alive.

OS will be listed.

Duration of Response

DOR will be computed for subjects who have been identified as a responder (achieved an overall response of CR or PR according to RECIST v1.1 during the PFS observation period); it will be computed as described in Section 5.3, where the reference date will be the first date where a subject has been documented to have achieved a responder designation. Censoring algorithms similar to those identified for PFS will be used for DOR.

DOR will be listed.

7.3. Additional Efficacy Endpoints and Analyses

Efficacy endpoints ORR, DCR, DOR and PFS defined according to irRECIST will not be derived.

8. PHARMACOKINETICS/PHARMACODYNAMICS

NA

9. QUALITY OF LIFE

NA

10. SAFETY

All safety analysis reporting will be based on the SAF.

10.1. Adverse Events

AEs will be recorded from the time of first study drug administration until 28 days after the last dose of study drug or until a subject initiates a new cancer therapy, whichever is earlier. AEs will also be assessed for severity using the NCI-CTCAE v. 4.03, relationship to each therapy (Definitely Related, Probably Related, Possibly Related, Unlikely Related, Not Related), and seriousness (Yes, No). AEs will be considered treatment-emergent if their onset occurs within the on-therapy period. Summary of events related to any study treatment will be provided.

An overview of treatment-emergent AEs (TEAEs) will be produced, including counts and percentages of subjects with any incidences of: TEAEs, CTCAE Grade 3 or higher TEAEs, TEAEs related to study treatment, CTCAE Grade 3 or higher TEAEs related to study treatment, serious adverse events (SAEs), TEAEs leading to study drug discontinuation, infusion-related reactions (IRRs), and fatal TEAEs.

A separate overview of AEs identified as IRRs related to CRS-207 will be provided. This display will include the number of infusions received by subjects, the number of subjects having an IRR, total number of IRRs per subject, maximum IRR grade, and dose modifications resulting from IRRs.

Adverse events will be coded based on the Medical Dictionary for Regulatory Affairs (MedDRA) for reporting by system organ class (SOC) and preferred term (PT) in descending order of overall incidence. For these summaries, subjects with multiple AEs with the same SOC and/or PT will only be counted once at each level of summarization.

Summaries of adverse events by SOC and PT will include the following types:

- TEAEs;
- TEAEs related to any study treatment (Definitely Related, Probably Related, or Possibly Related);
- CTCAE Grade 3 or higher TEAEs;
- CTCAE Grade 3 or higher TEAEs related to any study treatment;
- CRS-207 infusion-related reactions;
- SAEs.

To account for potential differences in the extent of exposure between the treatment categories, a subject-year adjusted rate will also be presented. The rate is calculated as the number of subjects with an event divided by the total subject-years of safety observation, where subject-years of safety observation for each subject is defined as duration of safety observation (defined in Section 5.3) in days divided by 365.25.

A comprehensive listing of all AEs will be provided in a by-subject data listing, this will include information on:

- SAEs;
- TEAEs leading to treatment discontinuation; and
- Fatal AEs (with identification of those which occur within the on-therapy period).

Unacceptable Toxicities

Subjects will be monitored for unacceptable toxicities during the Safety Run-in Period [the first 28 days (through 7 days after the Cycle 2 dose)]. Unacceptable toxicities will be presented in the AE data listing.

Deaths

The number and percent of subjects who died along with primary cause of death will be summarized overall (including the post-study survival surveillance period) and within 28 days of last dose of study drug. All death data will be listed.

10.2. Clinical Laboratory Evaluations

Clinical chemistry and hematology parameters will be reported based on the International System of Units (SI). The following laboratory evaluations will be reported in data summaries, with asterisks (*) indicating those that will be graded using NCI-CTCAE:

Hematology: Hematocrit, white blood cell (WBC)*, absolute neutrophil count*, lymphocytes*, hemoglobin*, monocytes, eosinophils, basophils, red blood cell (RBC), and platelet count*

Clinical chemistry: sodium*, potassium*, chloride, bicarbonate, glucose*, blood urea nitrogen (BUN), creatinine*, lactate dehydrogenase, alanine aminotransferase (ALT)*, aspartate aminotransferase (AST)*, alkaline phosphatase*, bilirubin (total*, direct, indirect), total protein, albumin*, calcium, magnesium*, phosphate*, and uric acid.

Thyroid function: Thyroid stimulating hormone, T3, FT3, FT4.

Shift tables displaying the shift from baseline to the worst value of NCI-CTCAE grade will be presented based on the most extreme change as it relates to the relevant NCI-CTCAE definition. NCI-CTCAE relating to “high/hyper” conditions will depend on the maximum post-baseline value while NCI-CTCAE “low/hypo” will be reported based on the minimum post-baseline value. Separate shift tables will be prepared for parameters with bi-directional toxicity grading.

All laboratory parameters will be provided in subject data listings.

10.3. Other Safety Evaluations

Vital Signs

Vital signs include: respiratory rate (bpm); temperature (°C); systolic and diastolic blood pressure (mmHg); pulse (bpm); pulse oximetry (%); height (cm) and weight (kg).

Vital sign data will be provided in data listings.

ECOG Performance Status

ECOG data will be listed.

Electrocardiogram (ECG)

Electrocardiogram (ECG) parameters include: HR (bpm), PR (msec), QRS (msec), QT (msec), QTcF (msec) and QTcB (msec). Observed values and changes from baseline for ECG parameters will be listed.

Physical Examinations

Physical examinations will be presented in subject data listings.

11. CHANGES TO THE PLANNED ANALYSIS

All efficacy endpoints will be derived and listed for each subject, but will not be summarized.

12. REFERENCES

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13. APPENDICES

13.1. Table of Contents for Tables

13.2. Table of Contents for Listings

13.3. Table of Contents for Figures

No figures planned.