Official Title of Study:

A PHASE 1/2, MULTICENTER, OPEN-LABEL, DOSE FINDING STUDY TO ASSESS THE SAFETY, TOLERABILITY, AND PRELIMINARY EFFICACY OF CC-122 IN COMBINATION WITH NIVOLUMAB IN SUBJECTS WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA (HCC)

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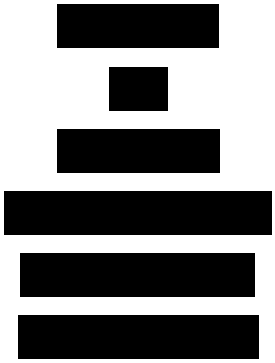
STATISTICAL ANALYSIS PLAN

A PHASE 1/2, MULTICENTER, OPEN-LABEL, DOSE FINDING STUDY TO ASSESS THE SAFETY, TOLERABILITY, AND PRELIMINARY EFFICACY OF CC-122 IN COMBINATION WITH NIVOLUMAB IN SUBJECTS WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA (HCC)

STUDY DRUG: CC-122

PROTOCOL NUMBER: CC-122-HCC-002

DATE FINAL: **30APR2020**



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1. LIST OF ABBREVIATIONS

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	Adverse events
AFP	Alpha-fetoprotein
ATC	Anatomical Therapeutic Chemical
AUC	Area under the concentration-time curve
BCLC	Barcelona Clinic Liver Cancer
BE	Biomarkers evaluable
BLQ	Below the limit of quantification
BMI	Body mass index
BNP	Brain natriuretic peptide
BOR	Best overall response
BPM	Breathes per minute
bpm	Beats per minute
CBC	Complete blood count
CI	Confidence interval
CL/F	Apparent clearance of drug from plasma after extravascular administration
C_{max}	Maximum observed concentration
CR	Complete response
CRBN	Cereblon
CSR	Clinical study report
CT	Computed tomography
CV%	Coefficient of variation
DBP	Diastolic blood pressure
DCR	Disease control rate
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
ECGs	Electrocardiograms
ECHO	Echocardiogram

Abbreviation or Specialist Term	Explanation
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EE	Efficacy evaluable
EOT	End of treatment
FCBP	Females of child bearing potential
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin embedded
GCP	Good Clinical Practice
GM-CSF	Granulocyte-macrophage colony stimulating factor
HBcAb	Hepatitis B core antibody
HBeAb	Hepatitis B e antibody
HBeAg	Hepatitis B e antigen
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HCVAb	Hepatitis C virus antibody
ICH	International Conference on Harmonisation
IFN-γ	Interferon-gamma
IHC	Immunohistochemistry
IL	Interleukin
IP	Investigational product
irBOR	irRECIST best overall response
irDCR	irRECIST disease control rate
irNN	irRECIST irNon-CR/Non-PD
irORR	irRECIST objective response rate
irPD	irRECIST progressive disease
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
IV	Intravenously
LLOQ	Lower limit of quantification
LoD	Limit of detection

Abbreviation or Specialist Term	Explanation
LVEF	Left ventricular ejection fraction
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
MEFL	Molecules of equivalent fluorescent label
Min	Minimum
MTD	Maximum tolerated dose
MUGA	Multi-gated acquisition
NCA	Non-compartmental analysis
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ND	Not done
NE	Not evaluable
NTD	Non-tolerated dose
ORR	Objective response rate
OS	Overall survival
PBMC	peripheral blood mononuclear cells
PD	Progressive disease
PFS	Progression free survival
PI	Principal investigator
PK	Pharmacokinetics
PPRMP	Pregnancy Prevention Risk Management Plans
PR	Partial response
PT	Preferred Term
PTT	Partial thromboplastin time
QNS	Quantity not sufficient
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Stable disease

Abbreviation or Specialist Term	Explanation
SMQ	Standardized MedDRA Queries
SOC	System organ class
SRC	Safety Review Committee
$t_{1/2}$	Terminal half-life
TCR	T cell receptor
TEAE	Treatment-emergent adverse events
T_{max}	Time to maximum concentration
TMTB	total measured tumor burden
TNF-α	Tumor necrosis factor alpha
TTP	Time to progression
ULN	Upper limit of normal
ULOQ	Upper limit of quantification
Vz/F	Apparent volume of distribution
WBC	White blood cell
WHO	World Health Organization
WHODrug	World Health Organization Drug Dictionary

[redacted]

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objective of the Phase 1 portion (dose finding) of the study is:

- To evaluate the safety and tolerability of CC-122 when administered orally in combination with Nivolumab and to define the RP2D

The primary objective of the Phase 2 portion (dose expansion) of the study is:

3.2. Secondary Objectives

The secondary objectives of the entire study are:

- To evaluate the preliminary efficacy of CC-122 in combination with Nivolumab based on various endpoints by RECIST 1.1
- To evaluate the pharmacokinetics (PK) of CC-122 in subjects coadministered multiple doses of CC-122 with Nivolumab
- To determine Nivolumab PK when coadministered with CC-122

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

CC-122-HCC-002 is a Phase 1/2 dose escalation and expansion clinical study of CC-122 in combination with Nivolumab in subjects with unresectable HCC who have progressed after or were intolerant to no more than 2 previous systemic therapies for unresectable HCC or are naïve to systemic therapy.

The dose escalation part of the study will explore 1 or more dose levels of CC-122 in combination with Nivolumab using a modified dose escalation (3+3) design (Storer,1989), followed by an expansion part once the RP2D is defined.

The study is designed to explore three dose levels, to identify the RP2D, and is not required to escalate to a nontolerated dose (NTD) or maximum tolerated dose (MTD). CC-122 will initially be administered orally 5 consecutive days out of 7 (5 days on/2 days off weekly) on Days 1 to 5, 8 to 12, 15 to 19 and 22 to 26 of each 28-day cycle. The investigated starting daily dose of CC-122 will be 2.0 mg, and two subsequent dose levels (3.0 and 4.0 mg) are planned to be evaluated based on evaluation of pre-specified dose limiting toxicities (DLTs). The study intends to identify the RP2D at or below the 4.0 mg dose level, however intermediate dose levels, or a higher dose level, may be evaluated at the discretion of the Safety Review Committee (SRC). Dose escalation to the intermediate or higher dose levels of CC-122 will not exceed 50% of the previously established tolerable dose level. Smaller dose increments based on toxicity, PK profile and pharmacodynamic findings may be evaluated, if necessary. Nivolumab will be administered at the dose of 3.0 mg/kg intravenously (IV) every 2 weeks. Once the RP2D for dosing of CC-122 in combination with Nivolumab is defined, expansion (Phase 2) will start.

A modified 3+3 dose escalation design will be used to identify the initial toxicity of the combination. Up to six subjects will be concurrently enrolled onto a dose level. Decisions as to which dose level to enroll a new subject will be based on the number of subjects enrolled and evaluable, the number of subjects experiencing DLTs, and the number of subjects enrolled but who are not yet evaluable for toxicity in the current cohort at the time of new subject entry.

A dose is considered an NTD if 2 or more out of up to 6 evaluable subjects in a cohort experience a DLT in Cycle 1. During dose escalation, the decision to either evaluate a higher dose level, an intermediate dose level, or declare the RP2D dose (or if applicable, NTD) will be determined by the SRC, based on their review of all available clinical data, PK, pharmacodynamic and laboratory safety data for a given dose cohort.

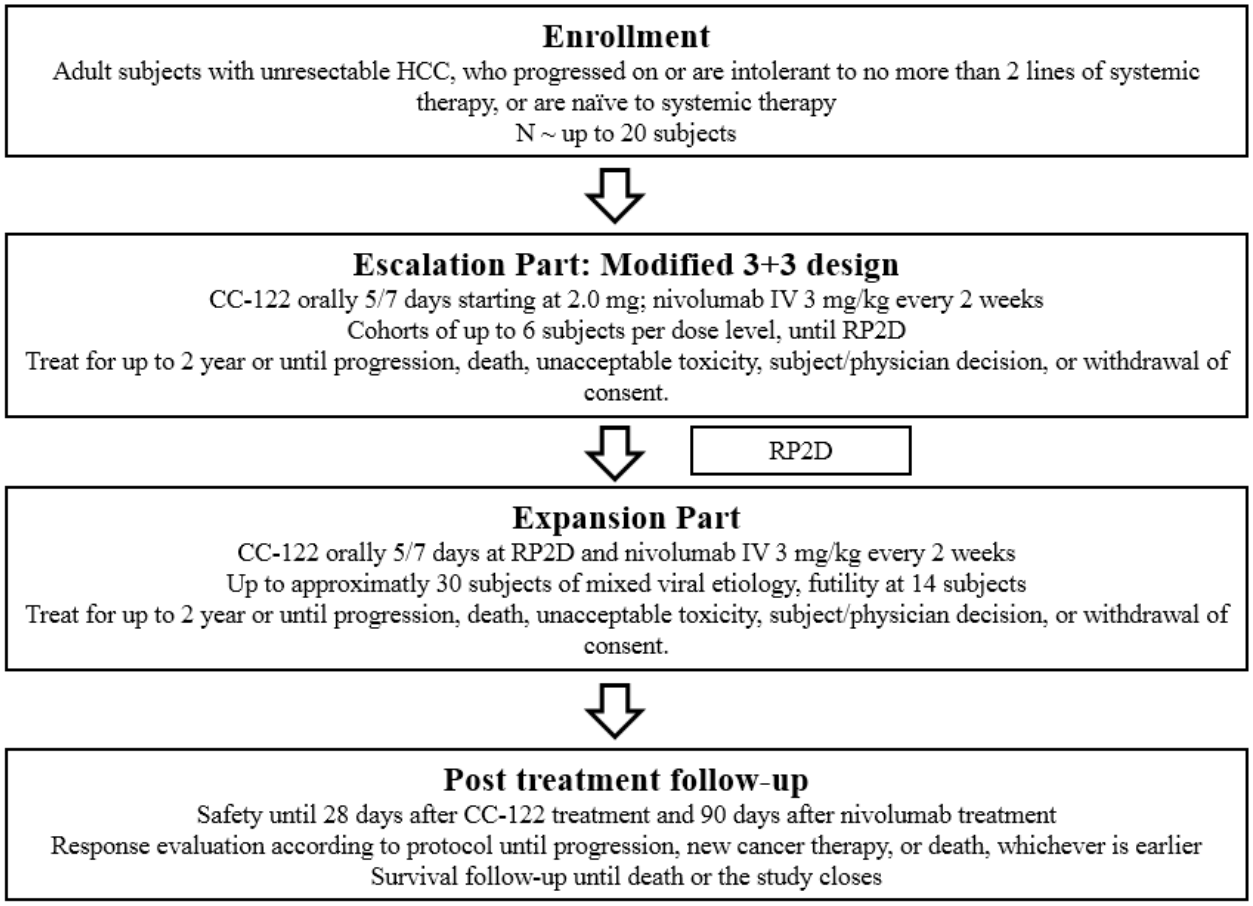
Non-evaluable subjects will be replaced at the discretion of the SRC.

Following completion of the dose escalation part (Phase 1), up to 30 additional subjects will be enrolled in an expansion part (Phase 2). A futility analysis will be conducted as follows. In the first 14 subjects treated, if no responder is observed out of 14 subjects then enrollment for the expansion cohort will stop for futility. Enrollment will continue during the evaluation of the 14 subjects. If $\geq$ 1 subject out of 14 responds (Complete Response [CR] or Partial Response [PR]), then approximately 30 total subjects will be enrolled in the Phase 2 portion. The SRC will

continue to review safety data regularly throughout the study and make recommendations about study continuation and dose modification, as appropriate.

The study will be conducted in compliance with International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/ Good Clinical Practices (GCPs).

Figure 1: Overall Study Design



HCC = hepatocellular carcinoma; IV = intravenous; RP2D = Recommended Phase 2 Dose.

4.2. Study Endpoints

Table 2: Study Endpoints

Endpoint	Name	Description	Timeframe
Primary Phase 1	The incidence of DLTs and the incidence and severity of treatment-emergent adverse events (TEAEs)	See Section 7.6 of protocol for the definition of DLTs	Dose Escalation Phase
Primary Phase 2	Preliminary efficacy as measured by ORR	The combined incidence of CR + PR, by investigator assessment of response by RECIST 1.1	Dose Escalation and Dose expansion Phase
Secondary	Preliminary efficacy	Disease control rate (DCR), duration of response (DoR), progression free survival (PFS), overall survival (OS), and time to progression (TTP) based on investigator assessment of response using RECIST 1.1 guidelines	Dose Escalation and Dose expansion Phase
Secondary	Plasma PK parameters	Including but not limited to maximum observed concentration (C_{max}), area under the concentration time curve (AUC), time to maximum concentration (T_{max}), terminal half-life ($t_{1/2}$), apparent total body clearance (CL/F) and apparent volume of distribution (Vz/F) for CC-122 and Nivolumab after multiple dose administration	Dose Escalation Phase
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]

Endpoint	Name	Description	Timeframe
[redacted]	[redacted]		[redacted]

4.3. Stratification, Randomization, and Blinding

This study is an open-label study. Treatment assignment does not require randomization, blinding or stratification.

[redacted]

[redacted]	[redacted]	[redacted]			
		[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

5. GENERAL STATISTICAL CONSIDERATIONS

5.1. Reporting Conventions

5.1.1. General Reporting Conventions

General reporting conventions for this study are:

- By default, descriptive statistics include: n (the corresponding sample size), Mean, Median, Standard Deviation, Minimum (Min), and Maximum (Max). Unless specified in the actual table shells, the mean, median, and the upper and lower limits of a 2-sided 95% confidence interval (CI) should be displayed to one more decimal place than the original data (derived analysis data). Standard deviation and standard error should be formatted to two more decimal places than the measured value. The minimum and maximum should be displayed to the same number of decimal places as the original data.
- P-values will be presented with 4 decimal places.
- Summary tables, listings, and any supportive SAS output will include a "footer" of explanatory notes that will indicate, at a minimum, the following:
    - Program and data source (e.g., SAS program, including the path that generates the output).
    - Data extraction date (e.g., the database lock date, run date). The purpose of showing the data extraction date is to link the output to a final database, either active or archived, that is write-protected for replication and future reference.
    - Output date (appearing on each output page). The output date will indicate the date the output was generated by the analysis program.
- Individual subject listings will display all data supporting corresponding tables and figures.
- If the end of treatment (EOT) visit is performed on a date different from the date of any nominal visit, the nominal visit immediately after the EOT will be used for plotting. The data from the EOT visit will not be included for any parameter mean-over-time plot.

Other general conventions include:

For the dose escalation part, subjects will be grouped according to their initially assigned dose cohort. In dose expansion part, the subjects may be categorized into different subgroups, such as HCC etiology. In addition, subjects in the same subgroup at the same dose level from both study parts will be combined for analysis as appropriate. All analyses specified in this SAP will be summarized by dose cohorts in the dose escalation part by selected subgroups in the dose expansion part, by selected subgroup at the expanded dose with subjects and by study overall in the dose expansion part, unless specified otherwise.

5.1.2. General Definitions

General definitions for this study are:

- Where study drug or study treatment is referenced, this refers to Investigational Product (IP): CC-122 or Nivolumab, unless otherwise stated;
- The first dose date refers to the earliest dose of study drug and the last dose date refers to the latest dose of study drug.

5.2. Analysis Populations

5.2.1. Efficacy Evaluable (EE)

EE Population – All subjects who enroll, meet eligibility criteria, take at least 50% of both assigned IP in the first 2 cycles, have a baseline efficacy (tumor) assessment, and at least one post-baseline efficacy (tumor) assessment.

5.2.2. Enrolled

Enrolled Population – All subjects who are enrolled, i.e., all subjects who are assigned to study.

5.2.3. Safety

Safety Population – All subjects who enroll and take at least one dose of either IP i.e. have received at least one dose of CC-122 or Nivolumab.

5.2.4. Pharmacokinetics (PK) Evaluable

PK Evaluable Population – All subjects who enroll and receive at least one dose of either IP and have at least one measurable concentration of CC-122 or Nivolumab.

[redacted]

5.2.6. Reporting for Analysis Populations

In general,

- The Enrolled and Safety Populations will be used for the subject disposition.
- The demographic and baseline characteristics will be summarized on all Populations defined above.
- Drug exposure and all safety analyses (except for PK and biomarker) will be based on the Safety Population.
- Efficacy analyses (including Eastern Cooperative Oncology Group Performance Status [ECOG PS], except for PK or biomarker related endpoints) will be based on the Safety Population. Key Efficacy analyses [summary of ORR, DCR, DoR, PFS, OS and TTP] will be based on both the Safety Population and the EE Population. PK analyses will be based on the PK Population.

- [redacted]
- All listings will use the Enrolled Population unless otherwise stated.

6. SUBJECT DISPOSITION

The total number of screen failures with the reasons for failure will be summarized overall.

A summary of subject disposition will be presented by dose cohorts in dose escalation part by selected subgroups in dose expansion part, by selected subgroup at the expanded dose with subjects from both parts, and for the following analysis populations:

- Enrolled Population
- Safety Population

A tabulated summary of all analysis populations in Section 5.2 will be presented together with the subject disposition. A listing of whether a subject is excluded from those populations will be provided. A summary of subjects enrolled by site will be presented. A listing of subject enrollment (protocol version and date, informed consent date, and study phase assignment) will be provided.

Reasons for treatment discontinuation will be summarized separately for CC-122 and Nivolumab with the following categories:

- Adverse event
- Progressive disease
- Symptomatic deterioration
- Physician decision
- Withdrawal by subject
- Death
- Lost to follow-up
- Protocol violation
- Pregnancy
- Other

Reasons for discontinuation from the study will be summarized with the following categories:

- Adverse event
- Screen failure
- Withdrawal by subject
- Death
- Pregnancy
- Lost to follow-up
- Other

The following by-subject listing of subjects with demographic information attached will be provided:

- Subject listing of discontinuation
- Subject listing of screen failures
- Subject listing of visit completion
- Subject listing of previous participation

7. PROTOCOL DEVIATIONS/VIOLATIONS

The protocol violations and deviations will be identified and assessed by the clinical research physician or designee following company standard operational procedure. Protocol violations and protocol deviations will be summarized for the Enrolled Population.

A by-subject listings of subjects with protocol violations and deviations in the Enrolled Population will be provided.

8. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

The demographics and baseline characteristics will be summarized by dose cohorts in the dose escalation part by selected subgroups in dose expansion part, by selected subgroups at the expanded dose with subjects from both parts, and by study overall for all populations defined in Section 5.2. Individual subject listings for the Enrolled Population will be provided to support the summary tables.

8.1. Demographics

Age (years), height (cm), weight (kg) and Body Mass Index (BMI kg/m^2) will be summarized using descriptive statistics (e.g., n, mean, standard deviation, median, minimum, and maximum). Age is calculated based on the date of birth and the date of informed consent (if date of birth is not collected due to country specific regulations, the age recorded in the database will be used, see Section 17.2). Age category (≤65 versus >65 years), BMI category (< 20, ≥20 to <25, ≥25 to <30 and ≥30), sex, race, ethnicity and reproductive status (female of child bearing potential, female of non-childbearing potential) will be summarized with frequency tabulations.

BMI = Weight (kg) / (Height (m) x Height (m)).

8.2. Baseline Characteristics

Baseline clinical characteristics include the following parameters:

- Temperature (°C),
- Systolic Blood Pressure (SBP, mmHg),
- Diastolic Blood Pressure (DBP, mmHg),
- Pulse Rate (beats per minute [bpm]),
- ECOG PS
- Evidence of HCC diagnosis (Histological, Clinical and/or Radiologic),
- Barcelona Clinic Liver Cancer (BCLC) staging (B or C),
- Cirrhosis (Yes/No),
- HCC Risk Factor (alcohol, HBV, HCV, non-alcoholic steatohepatitis, unknown or other),
- Child-Pugh score (0-6),
- Baseline AFP level,
- Baseline HBV viral load,
- Baseline HCV viral load,
- Macroscopic Vascular Invasion (Yes/No),
- Extrahepatic Disease (Yes/No), and

- Hepatitis serology (Hepatitis B surface Antigen [HBsAg], Hepatitis B e Antigen [HBeAg], Hepatitis B surface Antibody [HBsAb], Hepatitis B e Antibody [HBeAb], Hepatitis B core Antibody [HBcAb] and/or Hepatitis C Virus Antibody [HCVAb]).

Categorical baseline variables will be summarized using frequency counts and percentage. Continuous baseline variables will be summarized by descriptive statistics in the same way as continuous demographic variables (e.g., n, mean, standard deviation, median, minimum, and maximum). Listings will be presented for the Enrolled Population.

8.3. Medical History

A summary table of medical history with frequency counts and percentage will be presented using Medical Dictionary for Regulatory Affairs® (MedDRA) system and system organ class (SOC) and preferred term (PT) for the Safety Population. Listings will be presented for the Enrolled Population.

8.4. Prior Therapies for This Disease

The number of prior therapies/surgeries will be summarized for prior radiation therapies, prior cancer surgeries, prior systemic anti-cancer therapies, prior hormonal anti-cancer therapies, prior stem cell transplants and prior locoregional therapy for this disease separately and overall by frequency tabulations for the Safety Population. The therapies/surgeries with the same sequence/regimen number are counted as one prior therapy/surgery. Listings of therapies for this disease will also be presented by categories (prior, concomitant, and follow-up) for the Enrolled Population. Prior therapies are the therapies that were started before the first dose of study drug. Concomitant therapies are the therapies that were started on or after the first dose of study drug, but on or before the last dose of study drug. Therapies in the follow-up are the therapies that were started after the last dose of study drug.

[redacted]

9. STUDY TREATMENTS AND EXTENT OF EXPOSURE

Study treatment and extent of exposure summaries will be provided based on the Safety Population. Descriptive statistics will be provided for treatment duration, number of days dosed, average length of cycle, average number of days dosed per cycle, number of cycles, number of subjects who entered each cycle, actual cumulative dose, average daily dose, actual dose intensity, and relative dose intensity and number of subjects who overdose by dose cohorts in the dose escalation part by selected subgroups in dose expansion part, by selected subgroup at the expanded dose with subjects from both parts, and by study overall.

9.1. Treatment Duration

For each subject and for each study drug, the treatment duration is defined as the length of time elapsed between the first and last non-zero and non-missing study drug dose date and including the duration between planned administration (i.e. rest period for CC-122 and time between last infusion and subsequent planned infusion for Nivolumab). The treatment duration is derived in days which are converted in weeks (by dividing the treatment duration by 7) for the summary.

The first study drug dose date is defined as the earliest date where study drug has been administered (i.e. the drug was administered and the actual dose is not null or zero).

The last study drug dose date is defined as the latest date where study drug has been administered (i.e. the drug was administered and the actual dose is not null or zero).

CC-122 (5/7-day schedule):

CC-122 treatment duration (days) =

(Last dose date of CC-122 in the study) – (First dose date of study drug in the study) + number of days in drug rest period +1.

The number of days in rest period to be added is 2 days for 5-days on 2-days off intermittent dose schedule.

Nivolumab:

Nivolumab treatment duration (days) =

(Last infusion start date of Nivolumab in the study) – (first dose date of study drug in the study) + days covered by last infusion + 1

The days covered by last infusion are 13 days with Nivolumab being administered every 2 weeks (Days 1 and 15).

9.2. Number of Days Dosed

For each subject and for each study drug, the number of days dosed is defined as the total number of days the subjects received a non-zero and non-missing dose.

CC-122 (5/7-day schedule):

CC-122 number of days dosed =

$$\sum \text{days with CC-122 non} - \text{missing and CC-122 non} - \text{zero dose}$$

Nivolumab:
Nivolumab number of infusions =

$$\sum \text{days with nivolumab non} - \text{missing and nivolumab non} - \text{zero dose}$$

9.3. Number of Cycles

For each subject and for CC-122, the number of cycles where CC-12 was administered will be summarized.

The number of cycles initiated will be equal to the last cycle number as recorded in the CRF. The number of cycles treated will be equal to the number of cycles dosed.

The detailed calculation of a cycle is described in Section 17.2.2.

9.4. Average Length of Cycle

For each subject and for CC-122, the average length of cycle is defined as the treatment duration in days divided by the number of cycles for each subject.

CC-122:
CC-122 average length of cycle (days) =

$$\frac{\text{CC} - 122 \text{ treatment duration (days)}}{\text{Number of CC} - 122 \text{ cycles dosed}}$$

9.5. Average Number of Days Dosed per Cycle

For each subject and for CC-122, the average number of days dosed per cycle is defined as the number of days dosed divided by the number of cycles for each subject; therefore it corresponds to the average number of days the subject was dosed in a cycle.

CC-122:
CC-122 average dose exposure per cycle (mg/cycle) =

$$\frac{\text{CC - 122 number of days dosed}}{\text{Number of CC - 122 cycles}}$$

9.6. Cumulative Actual Dose

For each subject and for each study drug, the cumulative actual dose is defined as the sum of all doses (actual) taken across the treatment period (i.e. across all cycles).

CC-122:
CC-122 cumulative actual dose (mg) =

$$\sum \text{CC - 122 doses}$$

Nivolumab

Nivolumab cumulative actual dose (mg/kg) =

$$\sum \text{nivolumab doses}$$

9.7. Average Daily Dose

For each subject and for CC-122, the average daily dose is defined as the cumulative actual dose divided by the number of days dosed.

CC-122:

CC-122 average daily dose (mg/day) =

$$\frac{\text{CC-122 cumulative actual dose}}{\text{CC-122 number of days dosed}}$$

9.8. Actual Dose Intensity

For each subject and for each study drug, the actual dose intensity is defined as the cumulative actual dose divided by the treatment duration (weeks).

CC-122:

CC-122 actual dose intensity (mg/week)=

$$\frac{\text{CC-122 cumulative actual dose}}{\text{CC-122 treatment duration (weeks)}}$$

Nivolumab:

Nivolumab actual dose intensity (mg/kg/week) =

$$\frac{\text{Nivolumab cumulative actual dose}}{\text{Nivolumab treatment duration (weeks)}}$$

9.9. Relative Dose Intensity

For each subject and for each study drug, the relative dose intensity is defined as actual dose intensity (dose/weeks) divided by expected dose intensity (dose/weeks) and expressed as a percentage. Relative dose intensity will be used for the measurement of study drug compliance.

CC-122:

As per the protocol, the expected dose intensity (dose/week) for each cohort is:

- For dose level -1: 5 mg/week,
- For dose level 1: 10 mg/week,
- For dose level 2: 15mg/week,
- For dose level 3: 20 mg/week.

CC-122 relative dose intensity (%)

$$\frac{\text{CC - 122 actual dose intensity (mg/week)}}{\text{CC - 122 expected dose intensity (mg/week)}} \times 100$$

Nivolumab

As per the protocol, the expected dose intensity (dose/week) for Nivolumab is fixed at 1.5 mg/kg/week.

Nivolumab relative dose intensity (%)

$$\frac{\text{Nivolumab actual dose intensity (mg/kg/week)}}{\text{Nivolumab expected dose intensity (mg/kg/week)}} \times 100$$

9.10. Dose Reduction/Interruption/Delay

For CC-122, dose reduction is defined as a decrease in dose (non-zero) between current and the immediately previous non-missing assigned dose (planned cohort dose level if the first dose) or between assigned dose and actual dose. Total days of dose reduction due to AE include all the days from the start of assigned dose decrease due to AE until either the assigned dose is changed (excluding missing values) or a new (non-missing) reason for assigned dose adjustment is entered, including the days with dose not administered, as well as those days when the actual dose administered is less than the assigned dose due to AE (count only once if redundant with the previous interval. Dose interruption occurs if the dose is not administered except as pre-specified by the protocol (i.e. rest period). If an interruption happens at the start of a cycle and causes a cycle to be postponed, it is also called dose delay. Consecutive doses not administered (including those separated by protocol planned rest period) with the same reason are counted as one interruption. The rest period between two consecutive dose interruptions due to AE will be included in the total days for that dose interruption.

For Nivolumab, a skipped infusion is defined as an infusion that is not administered at all before the subject discontinue from Nivolumab treatment. An incomplete infusion is defined as an infusion for which the actual dose administered is less than the dose assigned.

Dose reduction and interruption will be summarized and summaries will include:

For CC-122

- Frequency count of number of dose reductions;
- Frequency count of number of dose interruptions;
- Reason for dose reduction (including the reason for assigned dose adjustment and the reason for actual dose that is different from assigned dose);
- Reason for dose interruptions;
- Descriptive statistics of time to the first dose reduction (from the first dose);
- Descriptive statistics of time to the first dose reduction (from the first dose) due to an adverse event (AE) for those who have at least one dose reduction due to an AE;
- Descriptive statistics of time to the first dose interruption (from the first dose);

- Descriptive statistics of time to the first dose interruption (from the first dose) due to an AE for those who have at least one dose interruption due to an AE;
- Number and percentage of subjects who have ≥7 days of dose interruption due to an AE;
- Descriptive statistics of total days of dose reduction due to an AE for those who have at least one dose reduction due to an AE;
- Descriptive statistics of total days of dose interruption due to an AE for those who have at least one dose interruption due to an AE.

For Nivolumab

- Number of incomplete infusions;
- Number of skipped infusions;
- Reason for incomplete infusion;
- Reason for skipped infusion;
- Descriptive statistics of time to the first incomplete infusion (from the first dose);
- Descriptive statistics of time to the first incomplete infusion (from the first dose) due to an adverse event (AE) for those who have at least one dose reduction due to an AE;
- Descriptive statistics of time to the first skipped infusion (from the first dose);
- Descriptive statistics of time to the first skipped infusion (from the first dose) due to an AE for those who have at least one dose interruption due to an AE.

10. EFFICACY ANALYSIS

The efficacy endpoints of this study include ORR, DCR, DoR, PFS, TTP and OS. Tumor response and progression will be determined by the Investigator based on RECIST 1.1 [redacted]) as a primary guideline, and irRECIST ([redacted] as an exploratory assessment.

Tumor assessments will be performed at screening (up to 28 days before the Cycle 1 Day 1 [C1D1] dose), every 8 weeks (± 7 days) for the first 5 evaluations (10 months) and thereafter every 12 weeks (±7 days), regardless of treatment status. Tumor assessments should also be performed at any time, if clinically indicated. Tumor assessments should continue at the defined schedule until radiologic disease progression or new anticancer therapy, beyond the end of treatment if necessary.

Following disease progression, survival status will be determined approximately every 3 months thereafter until 2 years from enrollment, lost to follow-up, death or withdrawal of consent, whichever occurs sooner.

Survival follow-up may be conducted by record review (including public records) and/or telephone contact with the subject, family, or the subject's treating physician.

All summaries, analyses and figures of efficacy data will be presented as applicable by dose cohorts in dose escalation part, by selected subgroups in dose expansion part, by selected subgroup at the expanded dose with subjects from both parts, unless otherwise specified.

Individual listings of tumor assessment and derived endpoints will be provided, which include:

- For RECIST 1.1 and irRECIST, listing for total measured tumor burden (TMTB), including change (in mm and percentage) from baseline and change from nadir for each visit; the TMTB is calculated separately for target and new measurable lesions as the sums of the respective diameters of target and new measurable lesions; nadir is the smallest TMTB of all assessments since study treatment starts before the current assessment.
- Listing for non-target lesions (RECIST 1.1) and new non-measurable lesions (irRECIST);
- Listing of overall response by visit unconfirmed and confirmed best overall response (BOR) using RECIST 1.1;
- Listing of unconfirmed BOR using irRECIST;
- Listing of DoR, duration of Stable Disease (SD) and time to BOR (using RECIST 1.1);
- Listing of PFS, TTP (using RECIST 1.1) and OS with flags for the censored data;
- Listing of DoR, duration of Stable Disease (SD) and time to BOR (using irRECIST);
- Listing of PFS and TTP (using irRECIST) with flags for the censored data;

The detailed rules for using dates are described in Section 17.2.1.

10.1. Response Criteria

Investigators will use RECIST 1.1 and irRECIST to assess tumor response for subjects treated with CC-122 in combination with Nivolumab (see Table 4).

Table 4: Time Point Overall Tumor Response Definitions by RECIST 1.1 and irRECIST

Overall Response RECIST 1.1	**RECIST 1.1[1]**	**Overall Response irRECIST**	**irRECIST[2]**
CR	Disappearance of all target lesions, disappearance of all non-target lesions and normalisation of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis).	irCR	Complete disappearance of all measurable and non-measurable lesions. Lymph nodes must decrease to < 10 mm in short axis. Confirmation of response is not mandatory.
PR	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters, no unequivocal progression of non-target lesions and no new lesion(s), but the criteria for CR are not met	irPR	Decrease of ≥ 30% in TMTB relative to baseline, non-target lesions are irNN, and no unequivocal progression of new non-measurable lesions.
SD	Neither sufficient shrinkage in the sum of diameters of target lesions to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study, no unequivocal progression of non-target lesions and no new lesion(s).	irSD	Failure to meet criteria for irCR or irPR in the absence of irPD.
PD	At least a 20% increase in the sum of diameters of target lesions from nadir. In addition, the sum must also demonstrate an absolute increase of at least 5 mm, or unequivocal progression of non-target lesions, or appearance of new lesion(s).	irPD	At least 20% increase and minimum 5 mm absolute increase in TMTB compared to nadir, or irPD for non-target or new non-measurable lesions. Confirmation of progression is recommended minimum 4 weeks after the first irPD assessment.

Abbreviations: CR = Complete Response; PR = Partial Response; SD = Stable Disease; PD = Progressive Disease; ir=immune-related; irNN = irNon-CR/Non-PD, TMTB = total measured tumor burden,
[1] RECIST 1.1 overall response is based on the sum of diameters of the target lesions.
[2] irRECIST overall response is based on TMTB for target and new measurable lesions.

Table 5: RECIST 1.1 Best Overall Response When Confirmation of CR and PR is Required

Overall Response First Time Point	Overall Response Subsequent Time Point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD or PR[1]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

Abbreviations: CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = non evaluable.

[1] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the subject had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Note: All responses after first PD will not be considered as a response.

10.2. Best Overall Response (BOR)

Confirmed and unconfirmed BOR (or irBOR) will be summarized using frequency tabulation for the Safety Population and EE Population, separately.

Confirmed BOR will only be used to summarize ORR by RECIST1.1, with unconfirmed BOR used in the derivation of ORR, DCR, sustained DCR, DoR, duration of SD, PFS and TTP. Unconfirmed BOR will be used for graphs.

Figures of tumor assessment will be provided, which include:

- Waterfall plots: Each subject's best percent change as defined below will be represented by a bar, with a pattern specific to the dose cohort to which they were initially assigned to (in the dose escalation part) and designated subgroup (in dose expansion part), and with their overall relative dose intensity annotated below/above each bar. For each study phase, a separate graph on the next page will be produced.
    - For RECIST 1.1, a waterfall plot of best percentage change from baseline in the sum of diameters (longest for non-nodal lesions, short axis for nodal lesions) of target lesions for all subjects with non-missing target lesion.
    - For irRECIST, waterfall plot for best percent change from baseline in TMTB, for all subjects with non-missing TMTB.
- Spider plots: Each subject's percent change from baseline as defined below, will be represented by lines with a colour specific to the dose cohort to which they were initially assigned to (in the dose escalation part) and designated subgroup (in dose expansion part). For each phase, a separate graph on the next page will be produced.
    - For RECIST 1.1, a spider plot of percent change from baseline in target lesions by time from first dose.
    - For irRECIST, a spider plot of percent change from baseline in TMTB by time from first dose

Unconfirmed BOR - RECIST 1.1

Unconfirmed BOR is the best of overall response across all time points evaluated by investigator using RECIST 1.1 criteria as defined in Table 4. The order in which responses are rated are CR, PR, SD, Progressive Disease (PD), not evaluable (NE). BOR is derived from post-baseline responses up until the date of progression or data cut-off date if progression has not occurred prior to the cut-off date. For example, if a subject has overall responses of PR, SD and PD, the unconfirmed BOR would be PR.

Duration of SD must meet minimum duration for at least 6 weeks if the BOR is SD. If the minimum time for a best response of SD is not met, the subject's best response depends on the subsequent assessments.

For example:

- A subject who has SD at the first assessment, PD at the second but does not meet minimum duration for SD, will have a best response of PD. PD assessment does not

required to be confirmed. A subject who has SD at the first assessment and is then lost to follow-up would be considered not evaluable.

Confirmed BOR – RECIST 1.1

Confirmed BOR is derived using Table 5 to confirm the best response. Confirmation of response requires repeat assessment of response (CR or PR) at the next scheduled scan more than 4 weeks following the first assessment meeting response criteria. If best overall response is SD, it must meet the minimum duration of 6 weeks. If the minimum time for a best response of SD is not met, the subject's best response depends on the subsequent assessments.

irBOR – irRECIST

In irRECIST , the determination of the adaptation of the immune-related unconfirmed best overall response (irBOR) is the single best immune-related response of overall response across all time points (post-baseline) evaluated by investigator using irRECIST criteria defined in Table 4 . The order in which responses are rated are irCR, irPR, irSD, irPD, irNE. For example if a subject has overall responses of irPR, irSD and irCR, the unconfirmed irBOR would be irCR. The same minimum duration of SD required in RECIST 1.1 must be met if the best overall response is irSD.

Objective Response Rate (ORR) and Disease Control Rate (DCR)

Unconfirmed ORR, confirmed ORR, DCR and sustained DCR will be derived separately for investigator RECIST 1.1 and irRECIST assessment [redacted]

Table 6: ORR and DCR Derivation rules

Endpoint	Confirmed	Criteria	Derivation
ORR	Yes	RECIST 1.1	Confirmed BOR of CR or PR
	No	RECIST 1.1	Unconfirmed BOR of CR or PR
	No	irRECIST	Unconfirmed irBOR of CR or PR
DCR	No	RECIST 1.1	Unconfirmed BOR of CR, PR or SD
	No	irRECIST	Unconfirmed irBOR of CR, PR or SD
Sustained DCR	No	RECIST 1.1	Unconfirmed BOR of CR, PR or SD (duration of SD ≥ 16 weeks)
	No	irRECIST	Unconfirmed irBOR of CR, PR or SD (duration of SD ≥ 16 weeks)

Abbreviations: BOR = best overall response; CR = complete response, SD = stable disease, PR = partial response, ir = immune related
Note: the immune-related endpoints will be referred to as irORR, irDCR and sustained irDCR respectively.

Frequency count and percentage of subjects meeting the criteria of each of the endpoints defined in [redacted] will be provided. In addition, two-sided 95% Clopper-Pearson ([redacted]) exact CIs will be provided for each endpoint. The summaries and inferential statistics will be provided for the Safety Population and EE Population.

In dose expansion phase, a figure (similar to a forest plot) of the estimate and associated two-sided Clopper-Pearson ([redacted]) 95% CI will be provided for each endpoint defined in [redacted] using the Safety Population for selected subgroups. The figures will also be provided for the EE Population.

10.3. Duration of Response (DoR) and duration of SD

DoR and duration of SD are derived for RECIST 1.1 and irRECIST separately and are defined as per the rules in Table 7.

Table 7: DoR and Duration of SD Derivation Rules

Endpoint	Derivation	Common Censoring Rules
DoR	**For subjects with an unconfirmed BOR of PR or CR**: DoR is measured from the date the criterion is first met for CR/PR (whichever is first recorded) until the first date when PD is documented or death occurred.	If the subject is still alive and did not experience PD at the date of cutoff, DoR and duration of SD will be censored at the date of last adequate[1] post-baseline tumor assessment prior to the cutoff date. If a subject progresses or dies after an extended lost-to-follow up time (two or more missed assessments), DoR and duration of SD will be censored on the date of last adequate tumor assessment.
Duration of SD	**For subjects with an unconfirmed BOR of SD**: Duration of SD is measured from the first dose date (i.e. the first dose of CC-122 or Nivolumab whichever occurred first) until the first date when PD is documented or death occurred.	

Abbreviations: BOR = best overall response; CR = complete response, SD = stable disease, PD = progressive disease, PR = partial response.
[1] Adequate tumor assessment is defined as the latest tumor assessment which is not missing or recorded as "not done" or "not all evaluable".

The Kaplan-Meier estimate of median DoR and SD for both RECIST 1.1 and irRECIST along with a 2-sided 95% CI ([redacted]) will be provided by using Safety and EE Populations. The Kaplan-Meier estimate will only be provided for the phase and dose cohort/subgroup where the following conditions are met:

- DoR (RECIST 1.1): at least 3 subjects have unconfirmed DCR;
- DoR (irRECIST): at least 3 subjects have unconfirmed irDCR;
- Duration of SD (RECIST 1.1): at least 3 subjects with BOR of SD;

- Duration of SD (irRECIST): at least 3 subjects with irBOR of SD.

10.4. Time to Best Overall Response

Time to unconfirmed BOR is derived for RECIST 1.1 and irRECIST separately. The Kaplan-Meier estimate of median time to BOR for both RECIST 1.1 and irRECIST along with a 2-sided 95% CI [redacted]) will be provided in a table using Safety and EE Populations.

Time to the BOR is measured from first dose date to the earliest of unconfirmed BOR (or irBOR) (CR or PR) based on RECIST 1.1 (irRECIST respectively). A subject whose BOR has never reached the level of CR or PR will be censored on the date of his or her last adequate tumor assessment. Subjects without valid baseline or post baseline tumor assessments will be censored on the study discontinuation date. Any valid overall post-baseline tumor assessment (not missing or not recorded as "not done" or "not all evaluable") are considered adequate tumor assessments in this case.

10.5. Progression-Free Survival (PFS) and Time to Progression (TTP)

10.5.1. Progression-Free Survival (PFS)

PFS is defined as the time from the first dose date until tumor progression or death, whichever occurs first.

Based on Food and Drug Administration (FDA) Guidance ([redacted]) a subject who has neither progressed nor died or who progresses or dies after an extended lost-to-follow up time (two or more missed assessments) will be censored on the date of last adequate tumor assessment. Subjects without valid baseline or post-baseline tumor assessments will be censored on their first dose date (i.e. the first dose of CC-122 or Nivolumab whichever occurred first). Censoring rules are defined in Table 8.

For PFS by irRECIST, the date of progression is the first date of PD as defined under irRECIST.

Analysis of PFS will be provided for RECIST and irRECIST separately and be presented for the Safety and EE Populations. Median of PFS times will be calculated using the Kaplan-Meier method and the corresponding 95% CIs will be presented. The number of events, subjects censored, and the Kaplan-Meier estimates of PFS rates at the time points of 3 months (90 days) and 6 months (180 days), along with standard errors of rate estimates (Greenwood's formula, [redacted]) will also be provided.

Table 8: Progression and Censoring Rules for PFS Analysis

Situation	Date of Progression or Censoring	Outcome
No baseline assessment	Date of first dose of study drug	Censored
No progression	Date of last visit with adequate assessment	Censored
Treatment discontinuation for toxicity or other reason without progression	Date of last visit with adequate assessment	Censored
New anticancer treatment started with no claim of progression	Date of last visit with adequate assessment	Censored
Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits or after patient misses one assessment visit	Date of death	Progressed
Death or progression after an extended lost-to-follow up time (two or more missed assessments)	Last visit with adequate assessment	Censored

In dose expansion phase, for the Safety and EE Populations, Kaplan-Meier survival curves of PFS will be presented for RECIST 1.1 and irRECIST separately; subgroup will be presented in the same figure using different lines colour/symbol.

10.5.2. Time to Progression (TTP)

TTP is defined as the time from the first dose date (i.e. the first dose of CC-122 or Nivolumab whichever occurred first) until tumor progression; TTP does not include death. The censoring rules for TTP are the same as described for PFS, except deaths without progression are censored at the time of the date of last adequate tumor assessment.

For TTP by RECIST 1.1, a subject who has not progressed will be censored on the date of last adequate tumor assessment. Subjects without valid baseline or post-baseline tumor assessments will be censored on their first dose dates. Any valid overall post-baseline tumor assessment (not recorded as “not done” or “not all evaluable”) are considered adequate tumor assessments in this case.

For TTP by irRECIST, the date of progression is the first date of PD as defined under irRECIST. A subject who has not progressed or who progresses or dies after an extended lost-to-follow up time (two or more missed assessments) will be censored on the date of his or her last adequate tumor assessment. Subjects without valid baseline or post-baseline tumor assessments will be censored on their first dose dates (i.e. the first dose of CC-122 or Nivolumab whichever occurred first).

Analysis of TTP will be provided for RECIST and irRECIST separately and presented for the Safety and EE Populations. Median of TTP will be calculated using the Kaplan-Meier method and the corresponding 95% CIs will be presented.

10.6. Overall Survival (OS)

OS is measured as the time from the first dose to death from any cause. All deaths, regardless of the cause of death, will be included. Subjects who have no death reported (known to be still alive or lost to follow-up) will be censored at the last contact date the subject is known to be alive or the clinical cut-off date whichever is earlier. OS will be analyzed similarly to PFS but the OS rates at 6 months (180 days) and 12 months (360 days) will be provided (instead of the rates at 3 and 6 months) by phase, dose cohort and overall for the Safety and EE Populations. A Kaplan-Meier curve will be provided for the dose expansion phase similarly to the PFS figure.

11. SAFETY ANALYSIS

The purpose of this section is to define the safety parameters for the study and to summarize the safety result of the study. All summaries of safety data will be conducted using the Safety Population and will be presented by dose cohorts in the dose escalation part by selected subgroups in the dose expansion part, and by selected subgroup at the expanded dose with subjects from both parts. Safety measurements will include AEs, clinical laboratory information (including troponin-T and Brain natriuretic peptide [BNP]), vital sign measurements, 12-lead electrocardiograms (ECGs), left ventricular ejection fraction (LVEF) assessments, ophthalmological exam, and pregnancy status. Individual subject listings will be provided to support the tables.

If an EOT measurement is conducted for those subjects who discontinue from the study, the data from the EOT visit will be included as a separate visit in the summary table. In addition, the data from the EOT visit will also be included in plots for parameters of individual subjects over time.

11.1. Adverse Events

11.1.1. Summary of Adverse Events

AEs will be analyzed in terms of treatment-emergent adverse events (TEAEs) which are defined as any AEs that start between the date of first dose of study drug and 28 days after the last dose of CC-122 or 90 days after the last dose of Nivolumab, whichever is later. All AEs will be coded using the MedDRA® dictionary Version 21.0 or higher.

The incidence of TEAEs will be summarized by MedDRA SOC and PT. The intensity of AEs will be graded 1 to 5 according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03 or higher if possible. AEs that are not defined in the NCI CTCAE Version 4.03 or higher should be evaluated for severity/intensity according to Version 3.0. For all other AEs not described in the NCI CTCAE criteria, the intensity will be assessed by the investigator as mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening (grade 4) or death (grade 5).

If a subject experiences the same AE more than once with a different grade, then the event with the highest grade will be tabulated in “by grade” tables. If a subject experiences multiple AEs under the PT (SOC), then the subject will be counted only once for that PT (SOC). In addition, AEs with a missing grade will be presented in the summary table as a grade category of “Missing” and will not be imputed.

A summary table of the subject incidence rate in each of the following categories will be provided. In addition, a table for each of the following categories will be produced where the incidence rate will be tabulated by SOC and PT and provided.

- TEAEs;
- TEAEs related to CC-122, Nivolumab and study drugs (CC-122 and/or Nivolumab);
- TEAEs of NCI CTCAE grade 3 or 4 by maximum NCI CTCAE grade;

- TEAEs related to CC-122, Nivolumab and study drugs (CC-122 and/or Nivolumab) with NCI CTCAE grade 3 or 4 by maximum NCI CTCAE grade;
- Grade 5 TEAEs with death outcome;
- Grade 5 TEAEs with death outcome related to CC-122, Nivolumab and study drugs (CC-122 and/or Nivolumab);
- Serious TEAEs;
- Serious TEAEs related to CC-122, Nivolumab and study drugs (CC-122 and/or Nivolumab);
- TEAEs leading to discontinuation of CC-122, Nivolumab and both study drugs (CC-122 and Nivolumab);
- TEAEs related to CC-122 leading to discontinuation of CC-122 and both study drugs (CC-122 and Nivolumab);
- TEAEs related to Nivolumab leading to discontinuation of Nivolumab and both study drugs (CC-122 and Nivolumab);
- TEAEs related to study drugs (CC-122 and/or Nivolumab) leading to discontinuation of CC-122, Nivolumab, and both study drugs (CC-122 and Nivolumab);
- TEAEs leading to dose reduction of CC-122;
- TEAEs related to CC-122 leading to dose reduction of CC-122;
- TEAEs related to study drugs (CC-122 and/or Nivolumab) leading to dose reduction of CC-122;
- TEAEs leading to dose interruption of CC-122, Nivolumab and both study drugs (CC-122 and Nivolumab);
- TEAEs related to CC-122 leading to dose interruption of CC-122 and both study drugs (CC-122 and Nivolumab);
- TEAEs related to Nivolumab leading to dose interruption of Nivolumab and both study drugs (CC-122 and Nivolumab);
- TEAEs related to study drugs (CC-122 and/or Nivolumab) leading to dose interruption of CC-122, Nivolumab and both study drugs (CC-122 and Nivolumab);

As well as

- TEAEs by cycle of onset;
- TEAEs related to CC-122, Nivolumab and study drugs (CC-122 and/or Nivolumab) by cycle of onset;
- TEAEs by maximum NCI CTCAE grade;
- TEAEs related to CC-122, Nivolumab and study drugs (CC-122 and/or Nivolumab) by maximum NCI CTCAE grade;
- Common (≥10%) TEAEs;

- Common (≥10%) TEAEs related to CC-122, Nivolumab and study drugs (CC-122 and/or Nivolumab);
- The selected TEAEs of interest

Selected TEAEs/ serious AEs (SAEs) of interest as determined by the mechanism of action, known class effects, or TEAEs observed to date will be summarized by cohort and grade or as needed. Standardized MedDRA queries (SMQs) will be used in the search strategy for some of the selected AEs of interest, intending to aid in case identification. The groupings of selected AEs, described by one phrase or topic term will be determined by clinicians based on SMQ or relevant search terms and provided to the statistical team, prior to database lock. To facilitate clinical study report (CSR) writing, a summary table of selected TEAEs of interest by PTs will also be provided.

The following tabulated lists will be provided together with AE tables,

- List of subjects who died by phase, dose cohort/disease subtype, subject number, SOC, and PT.
- List of SAEs by phase, dose cohort/disease subtype, subject number, SOC and PT;
- List of TEAEs leading to permanent withdrawal of study drug by phase, dose cohort/disease subtype, subject number, SOC, and PT;

Individual subject listings of AEs and AESIs will be presented. In addition, following tabulated lists will be provided as well,

- List of TEAEs that fulfill any of the DLT (see section 11.1.2) criteria by phase, dose cohort, subject number, DLT term, SOC, and PT
- List of TEAEs with NCI CTCAE grade 3 or 4 by phase, dose cohort/disease subtype, subject number, SOC, and PT
- List of TEAEs leading to dose reduction and dose interruption of study drug by phase, dose cohort/disease subtype, subject number, SOC, and PT.

11.1.2. Dose-limiting Toxicities (DLTs)

DLT is defined as a treatment-related AE(s) occurring in Cycle 1 (including pre-dose assessments on Cycle 2 Day 1) that meets one of the criteria defined in the protocol. A summary table of DLTs will be presented for the dose escalation phase only by dose cohort including number and percentage of subjects having a DLT. The percentage of subjects having a DLT is based on the number of subjects in the DLT evaluable Population. DLT flag will be added to the listing of AEs.

In the dose escalation phase, a subject evaluable for DLT is defined as one who:

- Received at least 75% of the planned doses of CC-122 and of Nivolumab during Cycle 1 without experiencing a DLT, having been followed for the entire DLT assessment period (Days 1 to 28 of Cycle 1 including the pre-dose assessments specified for Day 1 of Cycle 2)

  or

- Experienced a DLT after receiving at least one dose of either IP.

Non-evaluable subjects will be replaced at the discretion of the SRC. Additional subjects within any dose cohort may be enrolled at the discretion of the SRC.

11.2. Clinical Laboratory Evaluations

Clinical laboratory results of interest include: chemistry (including troponin T and BNP), hematology (including PT/INR/PTT), immunology, thyroid functions and urinalysis. Clinical laboratory values will be graded according to NCI CTCAE version 4.03 or higher for applicable tests. Book or literature normal ranges will be used to determine the categories of High, Low, and Normal.

Lab results and change from baseline will be summarized by visit using descriptive statistics for continuous variables. Similarly, maximum and minimum post-baseline values and corresponding change from baseline values (including unscheduled visits) will be summarized using descriptive statistics.

Shift tables demonstrating the changes (low/normal/high) from baseline to worst post-baseline value will be displayed in cross-tabulations for categorical variables. Bidirectional shift tables (low and high) demonstrating the change of NCI CTCAE grades from baseline to worst post-baseline during the treatment period will also be presented. These will be presented in separate tables for low and high NCI CTCAE grades. Summaries of worst NCI CTCAE grade by cycle (up to and including cycle 6) and worst post-baseline NCI CTCAE grade will be provided.

Listings of clinical laboratory data with NCI CTCAE grades (if applicable) and abnormal flags (low or high) will be provided.

Listing of pregnancy status will be also provided.

For some key lab tests, spaghetti plots for individual subjects will be presented to show the pattern of the lab test values over time using the Safety Population. All non-missing lab test values including assessments at scheduled and unscheduled visits will be presented. The x-axis will be the scheduled visits, and the y-axis will be the exact values (unscheduled results will be associated with the scheduled visit they relate to). Value for the EOT visit will be included in spaghetti plots but will be displayed for the nominal visit equal to or immediately after the EOT visit. The mean plot lab test values for each dose cohort in the dose escalation part and for each subgroup in dose expansion part will also be provided.

11.3. Vital Sign Measurements

Vital sign values and change from baseline will be summarized using descriptive statistics for each visit. Similarly, maximum and minimum post-baseline values and corresponding change from baseline values (including unscheduled visits) will be summarized using descriptive statistics.

Shift tables demonstrating the changes (low/normal/high) from baseline to worst post-baseline value will be displayed in cross-tabulations. Normal ranges in Table 9 will be used to determine the categories of low, normal and high. A listing of vital sign results will be provided.

Table 9: Normal Ranges of Vital Sign Measurements

Test	Normal Range (Unit)
DBP	[60, 90] (mmHg)
SBP	[100, 140] (mmHg)
Pulse	[60, 100] (bpm)
Temperature	[35, 38] (°C)

11.4. Electrocardiograms (ECG)

ECG parameters (from central review) and change from baseline with two-sided 95% CI will be summarized for each timepoint using descriptive statistics. Similarly, maximum and minimum post-baseline values (including unscheduled visits) and corresponding change from baseline values will be summarized using descriptive statistics.

Post-baseline abnormal QTc (both QTcF and QTcB) values will be summarized using frequency tabulations for the following 5 categories separately: QTc >450 msec; QTc >480 msec; QTc >500 msec; QTc increase from baseline >30 msec; QTc increase from baseline >60 msec.

Shift from baseline to worst post-baseline in the overall ECG interpretation ('Normal' 'Abnormal, not clinically significant' and 'Abnormal, clinically significant' by investigator review or 'Normal' and 'Abnormal' by central review) by visit will be displayed in cross-tabulations.

The mean change from baseline for each cohort along with the t-test 2-sided 95% CI, and the raw values for each individual subject will be plotted against scheduled/unscheduled visit to show the trend. Listings of ECG by investigator and central review will be provided.

11.5. Left Ventricular Ejection Fraction (LVEF) Assessment

LVEF assessment values and change from baseline will be summarized for each visit using descriptive statistics. Similarly, maximum and minimum post-baseline values (including unscheduled visits) and corresponding change from baseline values will be summarized using descriptive statistics.

Shift from baseline to worst post-baseline in the overall LVEF interpretation ('Normal', 'Abnormal, not clinically significant' and 'Abnormal, clinically significant') will be displayed in cross-tabulations. A summary table of abnormal LVEF will be provided. The following categories will be used in the summary:

- ≥20% absolute drop from baseline in LVEF (%);
- ≤45% in LVEF (%) at any post-baseline assessment;
- ≥20% absolute drop from baseline in LVEF (%) or ≤45% in LVEF (%) at any post-baseline assessment.

A listing of LVEF will be provided as well.

11.6. Ophthalmologic Exam

Data collected for ophthalmologic exam will be listed.

12. PK AND BIOMARKER ANALYSES

12.1. PK and Exposure Response Analyses

12.1.1. PK Parameters

PK parameters will be estimated based on the PK Population. Actual sampling times will be used in the calculations of PK parameters by using non-compartmental analysis (NCA). The following plasma PK parameters will be summarized for CC-122 and Nivolumab.

C_{max}	Peak (maximum) plasma drug concentration
T_{max}	Time to peak (maximum) plasma concentration at steady state
AUC_t	Area under the concentration-time curve calculated to the last observable concentration at time t
AUC_{inf}	Area under the concentration-time curve calculated from time zero to infinity.
V_z/F	Apparent volume of distribution during the terminal (λ_z) phase after extravascular administration
CL/F	Apparent clearance of drug from plasma after extravascular administration
$t_{1/2}$	Terminal elimination half-life

The following PK parameters will be also calculated for diagnostic purposes and listed but not be summarized.

λz	Terminal elimination rate constant (first-order)
λ_z lower	Lower limit of time (h) included in the calculation of λ_z.
λ_z N	Number of data points used in the calculation of λ_z.
λ_z upper	Upper limit of time (h) included in the calculation of λ_z.
Rsq adjusted	Adjusted regression coefficient for calculation of λ_z.
AUC %Extrap	Percentage of AUC_∞ due to extrapolation from the time of the last measurable concentration to infinity.

12.1.2. Exposure vs. Dose

CC-122 and Nivolumab plasma concentrations will be summarized by phase, actual dose level (CC-122), visit, and nominal time points. Plasma PK parameters will be summarized by phase, actual dose level (CC-122) using descriptive statistics (N, mean, standard deviation, coefficient of variation [CV%], geometric mean, geometric CV%, median, min, and max). In general, geometric mean and the geometric CV (%) will be derived from non-zero concentration values.

Coefficient of variation CV (%) is calculated as follows: 100×(standard deviation/mean).

Geometric CV (%) is calculated as follows: CV (%)=100×$\sqrt{\exp(\hat{\sigma}^2)-1}$, where $\hat{\sigma}^2$denotes the variance of the log-transformed values.

The following figures will be provided by actual CC-122 dose levels:

- Individual subject's concentration (linear scale) over time spaghetti plot;
- Individual subject's concentration (semi-logarithmic scale) over time spaghetti plot;
- Mean and ± standard deviation of concentration (linear scale) over time plot;
- Mean and ± standard deviation of concentration (semi-logarithmic scale) over time plot.

In addition, scatter plots of log transformed AUC_t, AUC_∞, and C_{max} versus CC-122 dose will be presented.

12.1.3. Exposure vs. Efficacy and/or Safety Parameters

Analyses will be performed to assess the exposure-response relationship of CC-122 plasma exposure (e.g. C_{max}, and AUC) with key efficacy parameters (tumor burden reduction and tumor shrinkage). Graphical analyses of the data will be conducted to visualize potential trends between drug exposure and response.

[redacted]

[redacted]

[redacted]

12.3. Adjustment of Multiplicity

Not applicable for this study.

13. QUALITY OF LIFE ANALYSIS

Not applicable for this study.

14. INTERIM ANALYSIS

No formal interim analysis is planned.

15. CHANGES TO THE STATISTICAL ANALYSES SECTION OF THE PROTOCOL

1. The protocol defines "enrolled population" as "All subjects who meet all the inclusion/exclusion criterion and are eligible for the study." As written, this definition excludes those subjects who were enrolled into the study and later discovered to have not met an inclusion/ or met an exclusion criteria. In order to accurately reflect ALL subjects who were enrolled into the study, the definition of enrolled population is expanded to remove the inclusion/exclusion criteria caveat which include all subjects who were assigned an enrollment number. The enrolled subjects who did not meet inclusion/exclusion criteria will be captured as protocol violators, which will be reported separately in a listing of protocol violations.

2. Per study HODC (Hematology and Oncology Development Committee) decision, this study will not be moving into expansion phase, thus the analyses described in the protocol for expansion phase as well as the exploratory efficacy analyses limited by the data will not be performed.

3. The following exploratory objectives, originally described in the study protocol, are not considered in this SAP and will be described in separate reports, if applicable.

   - To determine the relationship between baseline gene expression profiling, deoxyribonucleic acid (DNA) mutations, T cell clonality and protein biomarker expression with clinical endpoints including tumor response, response duration and progression free survival (PFS)
   - To determine the relationship of CC-122 and Nivolumab pharmacodynamics (PD) biomarkers in peripheral blood and changes in immune markers in tumor to clinical endpoints including tumor response, response duration and PFS
   - To determine the relationship between the plasma concentrations of CC-122 and Nivolumab and [redacted]s, safety, and clinical endpoints

   Therefore, the corresponding analyses including the analysis [redacted] described in Section 9.9 of the protocol are not considered in this SAP.

4. Futility analysis is no longer planned in this study.

5. Shift tables for vital signs and LVRF are no longer needed in this study.

6. Treated Population has been changed to Safety Population. This change was made because regulatory guidance provides a definition for Safety Population (all patients who took at least 1 dose of study medication; [redacted]), which represents the same subject population in the CC-122-HCC-002 protocol named as the "Treated Population" (ie, all subjects who enroll and take at least one dose of either IP [CC-122 or nivolumab]). Food

and Drug Administration (FDA). Guidance for industry: Submitting Select Clinical Trial Data Sets for Drugs Intended To Treat Human Immunodeficiency Virus-1 Infection. Mar 2018.

7. Correlation analyses will no longer be performed.

8. A listing of AESIs will now be created along with the listing of AEs

9. Summary of number of subjects who overdose is added to section 9.

[redacted]

17. APPENDICES

17.1. Dose Escalation Rules

Table 10: Decision Rules for Rolling 6 Dose Escalation Design

Current Cohort Information			Enrolling Dose Level*		
No. Enrolled	No. with DLTs	No. Without DLT	No. Pending	MTD Not Exceeded	MTD Exceeded
2	0,1	Any	Any	n	
2	2	0	0	n-1	
3	0	0,1,2	3,2,1	n	
3	0	3	0	n+1	
3	1	0,1	2,1	n	
3	1	2	0	n	
3	≥2	Any	Any	n-1	
4	0	0,1,2	4,3,2	n	n
4	0	3	1	n	n
4	0	4	0	n+1	n
4	1	0,1	3,2	n	n
4	1	2	1	n	n
4	1	3	0	n	n
4	≥2	Any	Any	n-1	n-1
5	0	0,1,2	5,4,3	n	n
5	0	3,4	2,1	n	n
5	0	5	0	n+1	n
5	1	0,1	4,3	n	n
5	1	2	2	n	n
5	1	3,4	1,0	n	n
5	≥2	Any	Any	n-1	n-1
6	0	0,1,2	6,5,4	Suspend	Suspend
6	0	3,4	3,2	Suspend	Suspend
6	0	5,6	1,0	n+1	MTD**
6	1	0,1	5,4	Suspend	Suspend
6	1	2	3	Suspend	Suspend

Current Cohort Information			Enrolling Dose Level*		
No. Enrolled	No. with DLTs	No. Without DLT	No. Pending	MTD Not Exceeded	MTD Exceeded
6	1	3,4	2,1	Suspend	Suspend
6	1	5	0	n+1	MTD
6	≥2	Any	Any	n-1	n-1
* n is the current dose level of subjects enrolled; n+1 and n-1 represent dose level escalation and de-escalation, respectively. Enrollment will be suspended at where it is indicated.					
** MTD is claimed only when there are 6 evaluable subjects.					

17.2. Handling of Dates

Dates will be stored as numeric variables in the SAS analysis files and reported in DDMMMYYYY format (i.e., the Date9. datetime format in SAS). Dates in the clinical database are classified into the categories of procedure dates, log dates, milestone dates, outcome dates, and special dates.

- **Procedure Dates** are the dates on which given protocol-specified procedure are performed. They include the dates of laboratory testing, physical examinations, tumor scans, etc. They should be present whenever data for a protocol-specified procedure are present and should only be missing when a procedure are marked as NOT DONE in the database. Procedure dates will not be imputed.
- **Log Dates** are dates recorded in CRF data logs. Specifically, they are the start and end dates for AEs and concomitant medications/procedures. They should not be missing unless an event or medication is marked as *ongoing* in the database. Otherwise, incomplete log dates will be imputed according to the rules in Appendix 17.4. However, in listings, log dates will be shown as recorded without imputation.
- **Milestone Dates** are dates of protocol milestones such as randomization, study drug start date, study drug termination date, study closure date, etc. They should not be missing if the milestone occurs for a subject. They will not be imputed.
- **Outcome Dates** are dates corresponding to study endpoints such as survival, progression, etc. In most cases they are derived either from a milestone (e.g., the survival date is derived from the death date), or a procedure date (e.g., the progression date is derived from the date of the tumor scan that was used to determine progression). They may be subject to endpoint-specific censoring rules if the outcome did not occur, but are not otherwise subject to imputation.
- **Special Dates** cannot be classified in any of the above categories and they include the date of birth. They may be subject to variable-specific censoring and imputation rules.

Dates recorded in comment fields will not be imputed or reported in any specific format.

17.2.1. Calculation Using Dates

Calculations using dates (e.g., PFS, subject's age or relative day after the first dose of study drug) will adhere to the following conventions:

- Study days after the start day of study drug will be calculated as the difference between the date of interest and the first date of dosing of study drug plus 1 day. The generalized calculation algorithm for relative day is the following:
    - If TARGET DATE ≥ DSTART then STUDY DAY = (TARGET DATE – DSTART) + 1;
    - Else use STUDY DAY = TARGET DATE – DSTART.

  Note that Study Day 1 is the first day of treatment of CC-122. Negative study days are reflective of observations obtained during the baseline/screening period. Note: Partial dates for the first study drug are not imputed in general. All effort should be made to avoid incomplete study drug start dates.
- Age (expressed in days) is calculated: AGE = CONSENT – DATE of BIRTH + 1. In practice, age will be transformed to years by dividing the difference by 365.25 days, then truncating.
    - Preference is for using calculated age from clinical database. When not available, calculated age from CRF or IVRS may be used
    - Partial birth date: impute missing day as 15th of the month; impute missing month as July; set missing age for missing year
- Intervals that are presented in weeks will be transformed from days to weeks by using (without truncation) the following conversion formula:

  WEEKS = DAYS /7
- Intervals that are presented in months will be transformed from days to months by using (without truncation) the following conversion formula:

  MONTHS = DAYS /30.4167

17.2.2. Calculation of Cycles

The start date of each cycle is defined as the date when the subject receives CC-122 if they receive CC-122; otherwise the first date they received Nivo will be the start date in that cycle. After the start dates are determined, the end date of each cycle is defined as (start date of subsequent cycle-1). The end date of the last cycle will be the dose start date of last cycle + 27.

17.3. Baseline, Repeated Measurements, and End of Trial

The general conventions for handling baseline, repeated measurements, and EOT are provided below:

- Baseline for any clinical laboratory test, vital sign and ECOG performance status is defined as the last value of a specific endpoint measured before first dose of the earliest of CC-122 or Nivolumab;

- Baseline values for biomarkers in the study is defined as the average of all qualified values (as specified in Table 12 and Table 13) collected at screening and before first dose of the earliest of CC-122 or Nivolumab, including values from Cycle 1 Day 1 pre-dose (0 hr) and qualified unscheduled visits. Other pre-dose samples from on-treatment visits after the first dose of the IP will not be used to impute the study baseline value. In addition, for those biomarkers with measurements at multiple timepoints within a visit, the qualified pre-dose (0 hr) value will be used to calculate the change from pre-dose, percent of pre-dose and/or percent change from pre-dose for the post-dose time points from the same visit.
- When there are multiple values for any laboratory test (clinical) or vital sign collected at the same visit, the one with last/latest assessment time stamp will be used for data analysis.
- When there are multiple values for biomarker data collected at the same visit, the average will be used for data analysis.
- Baseline of ECG triplicate measurement is defined as the mean of the ECGs recorded prior to initiation of therapy. Hence the baseline ECG endpoint value is obtained by averaging the last 3 ECGs or whatever number is available before the first dose of study treatment (earliest of CC-122 or Nivolumab). If the ECG overall interpretation is different in the triplicate, the best value (i.e. the lowest one) at baseline and the worst value (i.e. the highest one) at post-baseline visits will be used in the shift tables. The overall interpretation is classified as (from lowest to highest) normal, abnormal not clinically significant and abnormal clinically significant.
- For repeat ECGs at a particular post-baseline visit, derive RR, QTcB, QTcF first for each measurement and then derive the average of heart rate, RR, PR, QRS, QT, QTcB, QTcF measurements from all repeat ECGs. The average will be used to compute the descriptive statistics for that visit and the worst value at that visit will be used in the shift tables.
- EOT assessment for a particular endpoint is defined as the last non-missing post-baseline assessment during the study period.

17.4. Date Imputation Guideline

This subsection gives guideline on imputation of complete or partial missing AEs start and/or stop dates.

17.4.1. Impute Missing Adverse Events/ Prior or Concomitant Medications

Incomplete Start Date:

Missing day and month

- If the year is the **same** as the year of the first dosing date (earliest of CC-122 or Nivolumab), then the day and month of the first doing date will be assigned to the missing fields.

- If the year is **prior to** the year of first dosing date (earliest of CC-122 or Nivolumab), then December 31 will be assigned to the missing fields.
- If the year is **after** the year of first dosing (earliest of CC-122 or Nivolumab), then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year are the **same** as the year and month of first dosing date (earliest of CC-122 or Nivolumab), then the first doing date will be assigned to the missing day.
- If either the year of the partial date is **before** the year of the first dosing date (earliest of CC-122 or Nivolumab) or the years of the partial date and the first dosing date are the same but the month of partial date is **before** the month of the first dosing date, then the last day of the month will be assigned to the missing day.
- If either the year of the partial date is **after** the year of the first dosing date (earliest of CC-122 or Nivolumab) or the years of the partial date and the first dose date are the same but the month of partial date is **after** the month of the first dosing date, then the first day of the month will be assigned to the missing day.
- If the stop date is not missing, and the imputed start date is after the stop date, the start date will be imputed by the stop date.

Missing day, month, and year

- No imputation is needed, the corresponding AE will be included as TEAE.

Incomplete Stop Date: If the imputed stop date is before the start date, then the imputed stop date will be equal to the start date.

Missing day and month

- If the year of the incomplete stop date is the **same** as the year of the last dosing date (latest of CC-122 or Nivolumab), then the day and month of the last dosing date will be assigned to the missing fields.
- If the year of the incomplete stop date is **prior to** the year of the last dosing date (latest of CC-122 or Nivolumab), or prior to the year of the first dosing date, then December 31 will be assigned to the missing fields.
- If the year of the incomplete stop date is **prior to** the year of the last dosing date (latest of CC-122 or Nivolumab), but is the same as the year of the first dosing date (earliest of CC-122 or Nivolumab), then the first dosing date will be assigned to the missing date.
- If the year of the incomplete stop date is **after** the year of the last dosing date (latest of CC-122 or Nivolumab), then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year of the incomplete stop date are the **same** as the month and year of the last dosing date (latest of CC-122 or Nivolumab), then the day of the last dosing date will be assigned to the missing day.
- If either the year of the partial date is **not equal to** the year of the last dosing date (latest of CC-122 or Nivolumab) or the years of the partial date and the last dosing date are the same but the month of partial date is **not equal to** the month of the last dosing date, then the last day of the month will be assigned to the missing day.

17.5. Laboratory Data Handling Rules

The following data handling rules for laboratory parameters are for data analysis purpose (tables and figures). All original data will be presented as is in the data listings.

Table 11: Data Handling Conventions for Laboratory Parameters

Case	Convention	Example Data
values recorded as "<xx"	Set the numerical value to one tenth less in the next digit/decimal point	Immunoglobulin M (Serum) recorded as "<0.20" (g/l), set the numerical value to 0.199
values recorded as ">xx"	Set the numerical value to one tenth more in the next digit/decimal point	Creatinine clearance recorded as "> 60" (ml/min), set the numerical value to 60.1

17.6. PK Data Handling

Values Below the Limit of Quantification or Missing

Pre-dose concentrations that are below the limit of quantification (BLQ) or missing will be assigned a numerical value of zero. A BLQ value that occurs between pre-dose and the first quantifiable concentration point will be assigned a numerical value of zero. A BLQ value that occurs between quantifiable concentration points will be treated as missing. If BLQ values occur at the end of the collection interval, they will be assigned a numerical value of zero, unless otherwise warranted by the concentration-time profile. A concentration of zero occurring after quantifiable concentrations will be considered as missing for the calculation of PK parameters. Concentrations assigned a value of missing will be omitted from the calculation of descriptive statistics. A concentration value of zero will be included for the computation of arithmetic mean, and a post-dosing zero concentration will be substituted with a 50% value of the low limit of quantification (LLOQ), for the computation of geometric mean. If 50% or more of the values are BLQ at one timepoint, the arithmetic mean, median, and geometric mean will be reported as BLQ, and other descriptive statistics will not be calculated.

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

17.8. Study Procedures

Table 14: Table of Events

	Screening Period		Treatment Period											Follow-up Period	Follow-up Period	
	Screening [a]	Cycle 1				Cycle 2					Subsequent Cycles		EOT			
Day [b]	-28 to -1	1 [c]	8	15	22	1	8	15	18	22	1	15		28 day follow-up	90 days follow-up	Disease Progression/ Survival/ Pregnancy
STUDY ENTRY																
Informed consent	X															
Pregnancy prevention counseling	Pregnancy risk counseling and education prior to dispensing of IP															
Demographics	X															
Prior cancer history	X															
Prior/post cancer therapies	X													At the same schedule as survival visits		
Complete medical history	X															
[redacted]	[redacted]	[redacted]														
[redacted]	[redacted]	[redacted]														
Inclusion/exclusion criteria	X															
SAFETY ASSESSMENTS																
Adverse event collection	Continuous starting after informed consent signature, until 28 days after last dose of CC-122 and 90 days after the last dose of Nivolumab or at any time afterwards if the PI feels the event is related to any IP															
Physical examination (source documented only)	X	X				X					X		X			

	Screening Period		Treatment Period											Follow-up Period	Follow-up Period	
	Screening [a]	Cycle 1				Cycle 2					Subsequent Cycles		EOT			
Day [b]	**-28 to -1**	**1 [c]**	**8**	**15**	**22**	**1**	**8**	**15**	**18**	**22**	**1**	**15**		**28 day follow-up**	**90 days follow-up**	**Disease Progression/ Survival/ Pregnancy**
Ophthalmologic exam	X	As clinically indicated														
Weight	X	X				X					X		X			
Height	X															
Vital signs	X	X [b]	X	X	X	X					X		X			
ECOG PS	X	X[a]				X					X		X			
CBC with differential	X (-14 to -1)	X[a]	X	X	X	X	X	X	X	X	X	X Cycles 3-6 only	X			
Coagulation: PT, INR, PTT	X (-14 to -1)	X[a]				X					X					
Troponin-T and BNP	X	X[a]	X	X	X	X					X		X			
Chemistry laboratory (fasting, routine)	X (-14 to -1)	X[a]	X	X	X	X	X	X		X	X		X			
Amylase, lipase, T3, CK, TSH, fT4, immuno-globulins (IgG, IgM and IgA only) and T cell subsets (CD4+ and CD8+)	X	X[a]		X		X		X			X		X			
HBV and HCV serologies (HBsAg, HBeAg, HBsAb, HBeAb, HBcAb, HCVAb)	X															
HCV viral load	X															
HBV viral load	X	If HBsAg and/or HBcAb positive at screening, on day 1 of each cycle and at EOT														

	Screening Period		Treatment Period											Follow-up Period	Follow-up Period	
	Screening[a]	Cycle 1				Cycle 2					Subsequent Cycles		EOT			
Day[b]	-28 to -1	1[c]	8	15	22	1	8	15	18	22	1	15		28 day follow-up	90 days follow-up	Disease Progression/ Survival/ Pregnancy
Urinalysis	X (-14 to -1)					X					X					
Triplicate 12-lead electrocardiogram	X	X	X	X	X	X					X		X			
LVEF	X										X every 3 cycles		X			
Serum β-hCG (in FCBP)	X (-14 to -1)	As PPRMP indicated – to be updated according to PPRMP														
Urine β-hCG (females of childbearing potential [FCBP] only)	X[d] (-14 to -1)	As PPRMP indicated – to be updated according to PPRMP														
EFFICACY ASSESSMENTS																
PK samples (Intensive or sparse, multiple time points)		X		X												
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]		[redacted]					
[redacted]	[redacted]															

	Screening Period		Treatment Period											Follow-up Period	Follow-up Period	
	Screening[a]	Cycle 1				Cycle 2					Subsequent Cycles		EOT			
Day[b]	**-28 to -1**	**1[c]**	**8**	**15**	**22**	**1**	**8**	**15**	**18**	**22**	**1**	**15**		**28 day follow-up**	**90 days follow-up**	**Disease Progression/ Survival/ Pregnancy**
Fresh paired tumor biopsy	X[f]								D18 (+/- 7 days, preferably after 3 continuous days of CC-122 administration)[g]							
Tumor evaluation (CT or MRI)	X (-28 to -1)	RECIST 1.1 and irRECIST algorithm: Every 8 weeks (±7 days) for the first 10 months, then every 12 weeks (±7 days), until death, lost to follow up, progression or start of new anticancer therapy. See Sections 6.5.1 and 6.5.2 in the protocol														
Alpha-fetoprotein	X	X				X					X		X			
INVESTIGATIONAL PRODUCT																
Administer CC-122		5/7 days continuously														
Administer Nivolumab		Q2W														
CC-122 accountability		X	X	X	X	X	X	X		X	X	X	X			
Nivolumab accountability		Q2W											X[h]			X[h]
FOLLOW-UP																
Survival follow-up																Every 3 months (+/- 7 days)

Abbreviations: β-hCG = beta human chorionic gonadotropin; BNP = brain natriuretic peptide; CBC = complete blood count; CK = creatine kinase; CT = computed tomography; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EOT = End of Treatment; FCBP = females of child bearing potential; FFPE = formalin-fixed, paraffin embedded; fT4 = free T4; HBV = hepatitis B virus; HBsAg = hepatitis B surface antigen; HBeAg = hepatitis B e antigen; HBsAb= hepatitis B surface antibody; HBeAb = hepatitis B e antibody; HBcAb = hepatitis B core antibody; HCVAb = HCV antibody; HCV = hepatitis C virus; IG = immunoglobulin; INR = international normalized ratio;

LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging;; PI = Primary Investigator; PK = pharmacokinetic; PPRMP = Pregnancy Prevention Risk Management Plan; PT = prothrombin time; PTT = partial thromboplastin time; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; TSH = thyroid stimulating hormone.

[a] All screening assessments must be performed prior to enrollment and subsequently treatment, however, these events may occur on the same calendar day as they are completed prior to enrollment.

[b] An administrative window of ± 3 days is permitted for all cycles except Cycle 1 Day 1 (C1D1).

[c] C1D1 assessment may be omitted if screening assessment performed within 72 hours of first dose with the exception of the pregnancy test, see footnote d.

[d] As per PPRMP, FCBP must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting CC-122. The first pregnancy test must be performed within 10-14 days prior to the start of CC-122 and the second pregnancy test must be performed within 24 hours prior to the start of CC-122. The subject may not receive CC-122 until the study doctor has verified that the results of these pregnancy tests are negative.

[redacted]

[f] Archival tumor tissue will be required only if fresh tissue is not evaluable at screening. See Sections 6.8.1 and 6.8.2 in the protocol.

[g] Sample may be collected on Day 18 ± 7 days of Cycle 2. The sample must be collected at 3 to 6 (±1) hours postdose. Due to the intermittent schedule of CC-122 administration, the sample should preferably be collected after at least 3 continuous days of administration.

[h] After discontinuation of Nivolumab, females of childbearing potential must use effective contraception for at least 5 months.

17.9. Guideline for Tumor Response Evaluation

17.9.1. Solid Tumor

Guidelines for the New Response Evaluation Criteria in Solid Tumors (RECIST 1.1) can be accessed online at the following address:

[redacted]

17.9.2. Immune-related Response Evaluation Criteria in Solid Tumors (irRECIST)

Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Adaptation of the Immune Related Response Criteria can be accessed online at the following address:

[redacted]