Protocol: DCC-2036-01-004

Official Title: An Open-Label, Multicenter, Phase 1b/2 Study of Rebastinib (DCC-2036) in Combination with Carboplatin to Assess Safety, Tolerability, and Pharmacokinetics in Patients with Advanced or Metastatic Solid Tumors

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STATISTICAL ANALYSIS PLAN
PHASE 1B/2

NCT #: NCT03717415

DATE OF PLAN:

April 12, 2022

BASED ON:

Protocol DCC-2036-01-004, Amendment 4 (February 24, 2020)

STUDY TITLE:

An Open-Label, Multicenter, Phase 1b/2 Study of Rebastinib (DCC-2036) in Combination with Carboplatin to Assess Safety, Tolerability, and Pharmacokinetics in Patients with Advanced or Metastatic Solid Tumors

SPONSOR:

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This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

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LIST OF ABBREVIATIONS

Below is a list of the abbreviation that will be used throughout this document.

Abbreviation	Definition
AE	Adverse event
AESI	Adverse events of special interest
AUC	Area under the plasma concentration-time curve
BID	Twice daily
CA-125	Cancer antigen-125
CBR	Clinical Benefit Rate
CI	Confidence interval
CR	Complete response
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30 item
FACT-G	Functional Assessment of Cancer Therapy - General
ICH	International Conference on Harmonization
IHC	Immunohistochemical
ISH	*In situ* hybridization
IV	Intravenous
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
MTD	Maximum tolerated dose
MUGA	Multigated acquisition
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCI-PRO-CTCAE	National Cancer Institute Patient Reported Outcomes Common Toxicity Criteria for Adverse Events
NE	Not evaluable
ORR	Objective response rate

OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetic
PO	Orally
PR	Partial response
PRO	Patient-reported outcome
PT	Preferred term
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SOC	System organ class
TEAE	Treatment-emergent adverse event
TTP	Time to progression
US	United States

1. INTRODUCTION

This statistical analysis plan (SAP) describes the methods to be used in the analysis of safety and tolerability data from clinical study protocol DCC-2036-01-004 entitled "An Open-Label, Multicenter, Phase 1b/2 Study of Rebastinib (DCC-2036) in Combination with Carboplatin to Assess Safety, Tolerability, and Pharmacokinetics in Patients with Advanced or Metastatic Solid Tumors" in order to answer the study objectives, which is based on Protocol Amendment 4 of the clinical study protocol, dated February 24, 2020. This study consists of two parts. The Dose Escalation phase will be conducted in approximately 4 centers in the United States (US) and the Dose Expansion phase will be conducted in up to 18 centers in the US.

The analyses in this SAP will be used to support an abbreviated clinical study report (CSR) that provides a comprehensive summary of safety. Efficacy will be summarized for participants in the Dose Expansion phase only using ORR only. All other efficacy parameters will be listed. Analyses of pharmacokinetic (PK), pharmacodynamic, pharmacogenomic, and patient-reported outcomes (PRO) data, if conducted, will be described in separate analysis plans.

Populations for analysis, data handling rules, statistical methods, and formats for data presentation are described within this document. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the abbreviated CSR for this trial. The SAP outlines any differences in data analysis methods relative to those planned in the study protocol. Any changes to the data analysis methods after the SAP is finalized will be described in the abbreviated CSR.

Formats for tables, listings, and figures are specified in a separate document.

2. STUDY OBJECTIVES

2.1. Dose Escalation

2.1.1. Primary Objectives

- To establish the MTD or RP2D of rebastinib and carboplatin in combination
- To evaluate the safety and tolerability of rebastinib when administered in combination with carboplatin

2.1.2. Secondary Objectives

- To assess the PK of rebastinib and carboplatin when administered in combination
- To assess the preliminary efficacy of rebastinib administered in combination with carboplatin

2.2. Dose Expansion

2.2.1. Primary Objectives

- To evaluate the ORR as the primary efficacy measure of rebastinib in combination with carboplatin
- To evaluate the safety and tolerability of rebastinib when administered in combination with carboplatin

2.2.2. Secondary Objectives

- To assess the PK of rebastinib and carboplatin when administered in combination
- To evaluate efficacy measures, such as progression-free survival (PFS), clinical benefit rate (CBR), response duration, time to response, time to progression (TTP), and overall survival (OS) of rebastinib in combination with carboplatin

2.3. Exploratory Objectives (Dose Escalation and Dose Expansion)

- Assess the quality of life impact of rebastinib administered in combination with carboplatin using patient-reported outcome (PRO) measures
- To evaluate changes in select blood and plasma biomarkers when rebastinib is administered in combination with carboplatin
- To evaluate changes in tumor tissue microenvironment (e.g., changes in the composition of infiltrating mononuclear cells) when rebastinib is administered in combination with carboplatin
- To assess polymorphisms in genes encoding drug metabolic enzymes and/or transporters involved in metabolism and disposition of rebastinib in combination with carboplatin

3. STUDY DESIGN OVERVIEW

3.1. Overall Study Design

This is an open-label Phase 1b/2 multicenter study in participants with advanced or metastatic solid tumors who have exhausted available, approved therapies and for which carboplatin is considered appropriate treatment. Adverse events (AEs) will be assessed, and laboratory values, vital sign measurements, and electrocardiograms (ECGs) will be obtained to evaluate the safety and tolerability of rebastinib when administered in combination with carboplatin.

Rebastinib will be administered orally (PO) twice daily (BID), and carboplatin will be infused once every 3 weeks. A dose of carboplatin will be calculated using the Calvert formula based on the target area under the plasma concentration time curve (AUC) on Day 1 of each cycle. Each cycle is 21 days, however, initiation of subsequent cycles after Cycle 1 is dependent upon carboplatin dosing.

The study consists of two parts: Dose Escalation and Dose Expansion.

3.1.1. Dose Escalation Phase

In the Dose Escalation phase, doses of rebastinib and carboplatin will be escalated using modified 3 + 3 dose escalation rules starting with rebastinib at 50 mg BID in combination with AUC5 of carboplatin. The next cohort is rebastinib at 100 mg BID with AUC5 of carboplatin. The third planned cohort will be rebastinib at 100 mg BID with AUC6 of carboplatin. Based on the safety and tolerability, other combinations of doses such as rebastinib at 50 mg BID with AUC6 of carboplatin may be evaluated if, at least, rebastinib at 50 mg BID with AUC5 of carboplatin is deemed safe. In addition, the rebastinib dose may be increased to 150 mg BID with AUC5 and/or AUC6 of carboplatin if 100 mg BID of rebastinib with AUC5 and AUC6 of carboplatin is tolerated. Alternatively, 75 mg BID of rebastinib may be evaluated if 100 mg BID is not tolerated and 50 mg BID is deemed as safe.

Dose escalation will proceed to the next dose level if no dose-limiting toxicity (DLT) is observed in a minimum of 3 participants completing 1 cycle. If a DLT is observed in only 1 participant in a cohort of 3 participants, an additional 3 participants will be enrolled up to a total of at least 6 participants at this dose level. Dose escalation will then only proceed if no more than 1 participant in the cohort of 6 participants has experienced a DLT during the first cycle of treatment in the Dose Escalation phase. If a DLT is observed in 2 or more participants in a cohort of 3 to 6 participants, dose escalation will stop.

The determination of the maximum tolerated dose (MTD) or recommended Phase 2 dose (RP2D) will be based on the safety and tolerability of at least 6 participants at a dose level of the combination. As necessary for evaluation of safety and tolerability, up to 12 participants may be enrolled per cohort. Enrollment of additional participants to further explore safety and tolerability may take place simultaneously while a cohort at the next dose level is enrolling participants in the Dose Escalation phase.

The MTD is defined as the highest dose level of rebastinib and carboplatin at which no more than 1 of 6 participants experiences a DLT during the first cycle. The RP2D will be a dose level of rebastinib and carboplatin deemed safe and tolerable on the basis of the totality of safety, tolerability, PK, and preliminary efficacy data. The RP2D will not exceed the MTD.

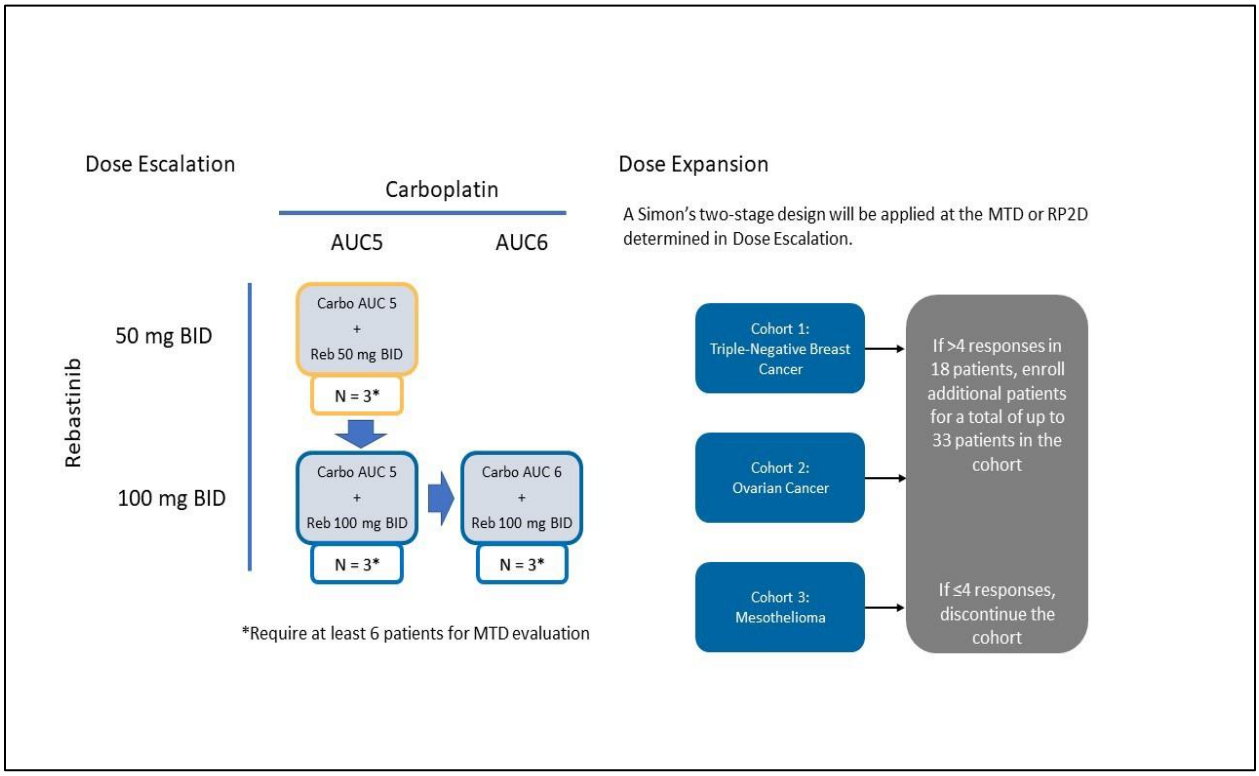
3.1.2. Dose Expansion Phase

The Dose Expansion phase will be initiated upon determination of the MTD or an RP2D in the Dose Escalation phase. In this phase, approximately 99 participants in three indication-specific cohorts will be enrolled with the RP2D. A Simon's two-stage design will be applied to further evaluate the safety, tolerability, and preliminary efficacy of rebastinib in combination with carboplatin in triple negative breast cancer (Cohort 1), ovarian cancer (Cohort 2), and mesothelioma (Cohort 3) participants. An RP2D used for each cohort will be chosen based on agreement between the Investigators and the Sponsor.

Each cohort in the Dose Expansion phase will initially enroll up to 18 participants in the first stage. The decision to enroll participants beyond the first stage will be based on response assessments obtained after the first post-dose response assessment of the last participant enrolled in the first stage of a cohort. Up to a total of 33 participants per cohort may be enrolled based on response assessments. If >4 responses (defined as unconfirmed partial response [PR] or complete response [CR] as best response) are seen in a cohort, additional participants will be enrolled for a total of up to 33 participants. If ≤4 responses are seen in a cohort, the cohort will be terminated. Participants who do not receive at least one dose of the combination will be replaced. In addition, if participants discontinued the study drug treatment prior to the scheduled, first post-dose tumor assessment (Cycle 3 Day 1) due to reasons other than disease progression (clinical or radiological) or an AE(s) at least possibly related to rebastinib, they may be replaced. Replaced participants will not be included in the responder analysis. There will be an enrollment pause between the first and second stage for evaluation of response.

The Study Schema for Dose Escalation and Dose Expansion are presented below:

Figure 1: Study Schema



3.2. Duration of Participation

Participants will receive study treatment until they develop progressive disease (PD), experience unacceptable toxicity, or withdraw consent. Participants will be eligible to receive study treatment as long as the Investigator and the Sponsor agree that the participant is showing clinical benefit, and for as long as rebastinib is being developed to support the indication, and continuation of treatment does not conflict with the Sponsor's right to terminate the study. After the participant discontinues treatment, the participant will be contacted via phone for safety follow-up. The study will end following the last participant's last visit.

3.3. Study Treatments

Rebastinib will be provided as tablets for oral administration containing 25 mg and 75 mg of active rebastinib. Rebastinib will be dosed BID continuously throughout each cycle. In the Dose Escalation phase, rebastinib will be escalated from 50 mg to 100 mg in combination with carboplatin. In addition, doses of 150 mg and 75 mg may also be explored.

Carboplatin will be administered by IV infusion over approximately 60 minutes on Day 1 of each cycle and at least 21 days apart. A carboplatin dose will be calculated using the Calvert formula. The maximum carboplatin dose should not exceed AUC (mg x min/mL) x 150 mL/min. Rebastinib will be administered prior to IV infusion of carboplatin. On Day 1 of Cycles 1 and 2 when serial PK samples will be collected, participants must take the dose of carboplatin 2 hours (+/-30 minutes) after rebastinib dosing.

In the Dose Escalation phase, carboplatin will be dose escalated from AUC5 to AUC6 to determine an RP2D of rebastinib and carboplatin combination. In the Dose Expansion phase, the MTD or an RP2D of carboplatin in combination with rebastinib will be administered. A different dose level not exceeding the MTD may be chosen for each cohort.

3.4. Planned Analyses

3.4.1. Interim Analyses

No formal interim analyses leading to an interim clinical study report are planned for this study.

Informal interim analyses are planned for each Expansion Cohort in the Dose Expansion phase after the first 18 evaluable participants have been enrolled and been followed for at least one post-baseline assessment. If 5 or more objective responses are observed according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) or modified RECIST (mRECIST) for pleural mesothelioma participants, then 15 additional participants will be enrolled into the expansion cohort. If 5 or more objective responses are observed prior to the enrollment of the 18th participant, then continued enrollment can proceed without a pause. Otherwise, a pause in an enrollment will occur until the 5th objective response is observed or the Expansion Cohort will be closed if less than 5 objective responses are observed.

3.4.2. Final Analyses

The final analysis will be conducted once all participants are off study.

3.5. Blinding

This is an open-label study.

3.6. Sample Size Considerations

Dose Escalation: The Dose Escalation phase will primarily be used to determine the MTD or an RP2D and evaluate the safety and tolerability of the combination using modified 3+3 dose escalation rules. Three dose escalation cohorts are planned, and an additional cohort may be added. Approximately 18 participants will be enrolled in the Dose Escalation phase.

Dose Expansion: A Simon's two-stage design will apply to this phase of the study. The number of participants required for each cohort was calculated to demonstrate 20% improvement in objective response rate (ORR) (from 20% historical ORR in the setting to 40% for the combination) under 80% power and one-sided alpha of 0.05. In the initial stage, up to 18 participants will be evaluated. Greater than 4 responses will be required to enroll additional participants to demonstrate the target efficacy of >10 responses in a total of 33 participants. Thus, this part of study may enroll approximately 99 participants (33 participants per indication-specific cohort). Participants who do not receive at least one dose of the combination will be replaced. In addition, if the study drug treatment is discontinued prior to the scheduled, first post-dose tumor assessment (Cycle 3 Day 1) due to reasons other than disease progression (clinical or radiological) or an AE(s) at least possibly related to rebastinib, participants may be replaced. Replaced participants will not be included in the responder analysis. For example, if 10% of participants will be replaced, approximately 110 participants may be enrolled.

4. STUDY ENDPOINTS

The following study endpoints are for the Dose Escalation and Dose Expansion phases.

4.1. Efficacy Endpoints

For efficacy endpoints based on imaging, RECIST v1.1 (Eisenhauer, Therasse and Bogaerts) will be used for all summaries except for participants with pleural mesothelioma. For participants with pleural mesothelioma, mRECIST will be used instead of RECIST v1.1 (Armato III and Nowak).

The primary endpoint in the Dose Expansion phase is the ORR, which is defined as the proportion of participants with a best overall response of CR or PR. Below is a list of the efficacy endpoints to be analyzed in this study.

4.1.1. Objective Response Rate

ORR is defined as the proportion of participants with best overall response of CR or PR according to RECIST v1.1 (or mRECIST for participants with pleural mesothelioma). Participants without a best overall response CR or PR will be considered as non-responders.

4.1.2. Clinical Benefit Rate

CBR at 6, 12, and 21 weeks is defined as proportion of participants with overall response of CR, PR, or stable disease (SD) at 6, 12, and 21 weeks. Participants without a CR, PR, or SD at the time point of interest (or a later time point) will be considered as not having clinical benefit at that time point.

4.1.3. Duration of Response

Duration of response (DOR) is defined as time from first PR or CR until the earliest documented evidence of PD or death due to any cause, whichever occurs first.

4.1.4. Time to Response

Time to response is defined as the time from first dose of study drug until to the first assessment demonstrating PR or CR.

4.1.5. Progression-Free Survival

PFS is defined as the time from first dose of study drug until the earliest documented evidence of PD or death due to any cause, whichever occurs first.

4.1.6. Time to Progression

TTP is defined as the time from first dose of study drug until the earliest documented evidence of PD.

4.1.7. Overall Survival

Overall survival (OS) is defined as the time from first dose of study drug until the date of death from any cause.

4.1.8. Cancer-Antigen 125 Response (ovarian cancer expansion cohort only)

Cancer-antigen (CA-125) response is defined as at least 50% reduction in CA-125 levels from baseline. The response must be confirmed and maintained for at least 28 days.

4.2. Safety Endpoints

The following will be evaluated as safety endpoints for the study:

- DLTs in the Dose Escalation phase
- AEs
- Serious adverse events (SAEs)
- Dose reduction or discontinuation of study drug due to toxicity
- Adverse events of special interest (AESIs)
  - Preferred term (PT) of 'muscular weakness' that is Grade 3 or higher
  - Lower level term of 'central retinal vein occlusion'
- Eastern Cooperative Oncology Group (ECOG) Performance Status
- Ophthalmologic examinations
- Changes from baseline in laboratory parameters
- ECGs
- Echocardiograms/multigated acquisition scans (MUGAs)
- Vital signs

4.3. Patient-Reported Outcomes

PROs will be assessed using the following questionnaires:

- The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30-item (EORTC-QLQ-C30). The EORTC QLQ-C30 is a validated, standardized, participant-completed questionnaire used extensively in international clinical studies.
- Assessment of the safety profile of rebastinib in combination with carboplatin using the National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (NCI-PRO-CTCAE).
- A "treatment-bother" question (GP5) from Functional Assessment of Cancer Therapy - General (FACT-G).

Analyses of PRO data, if conducted, are outside the scope of this SAP.

4.4. Pharmacokinetic Endpoints

PK endpoints when rebastinib is administered in combination with carboplatin and as a single agent include, but are not limited to:

- Time to maximum observed concentration (t_{max}: rebastinib only)
- Time to maximum observed concentration at steady state ($t_{max,ss}$: rebastinib only)
- Maximum observed concentration (C_{max})
- Maximum observed concentration at steady state ($C_{max,ss}$)
- Concentration observed at the end of the dosing interval (C_{min}, trough concentration)
- Concentration observed at the end of the dosing interval at steady state ($C_{min,ss}$)
- Area under the concentration-time curve (AUC)
- Half-life ($t_{½}$)
- Volume of distribution (V_d)
- Clearance (CL)

Analyses of PK data, if conducted, are outside the scope of this SAP.

4.5. Pharmacogenomic Endpoints

The pharmacogenomics endpoints of the study include:

- Assessment of polymorphisms in genes that may be associated with clinical response and/or study drug-related toxicity

Analyses of pharmacogenomic data, if conducted, are outside the scope of this SAP.

4.6. Biomarker and Pharmacodynamic Endpoints

The pharmacodynamic endpoints of the study include:

- Assess changes of serum chemokines/cytokines upon treatment
- Assess changes in monocyte population in peripheral blood
- Evaluate changes in tumor microenvironment, using tumor tissue, if obtained, including but not limited to tumor associated macrophage, tumor infiltrating lymphocytes using immunohistochemical (IHC), *in situ* hybridization (ISH), or other fit-for-purpose assays

Analyses of biomarker and pharmacodynamic data, if conducted, are outside the scope of this SAP.

5. DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

5.1. Definition of Baseline

Unless specified otherwise, baseline measurements are the most recent value prior to receiving the first dose of study drug.

5.2. Handling of Missing Data

Unless specified in the individual endpoint analysis, missing data will not be imputed except for the purpose of determining the date(s) of

- Initial diagnosis
- Prior medications or procedures
- AEs

Table 1: Partial or Missing Date Imputation Rules

Variable	Missing Day	Missing Day, Month	Missing Day, Month, Year
Date of Last Therapy/Date of Initial Diagnosis	Assign 1	Assign January 1 if prior to date of informed consent, otherwise use date of informed consent	Missing (do not impute)
Adverse Event Start Date	Assign first day of month unless it is the month of first dose of study drug. Otherwise, assign date of first dose of study drug or AE end date (if not missing), whichever is earlier.	Assign January 1 unless the year is year of first dose of study drug. Otherwise, assign date of first dose of study drug or AE end date (if not missing), whichever is earlier.	Assign date first dose of study drug.
Adverse Event/Medication/ Procedure End Date	Assign the last day of the month or end of study date or data cut-off date, whichever is earlier.	Assign December 31 or end of study date or data cutoff date, whichever is earlier.	If ongoing, end date is missing. Otherwise, assign end of study date or data cutoff date, whichever is earlier
Medication/Procedure Start Date	Assign 1 unless it is the month of first dose of study drug. Otherwise, assign date of first dose of study drug or imputed medication end date, whichever is earlier.	Assign January 1 unless the year is year of first dose of study drug. Otherwise, assign date of first dose of study drug or imputed medication end date, whichever is earlier.	Assign date first dose of study.

5.3. Study Visits

For safety parameters, unscheduled visits will be mapped to a scheduled visit if possible, using a window based on all the available actual visit dates for the scheduled visit. Data that are collected from unscheduled visits and cannot be mapped to a scheduled visit will not be included in the by-visit summary tables but will be presented in the listings. Early termination visits for safety measurements will not be mapped to any scheduled post-baseline visit but will be used as the last assessment during treatment period.

5.4. Study Day

If the date of interest occurs on or after the date of first dose of study drug, then study day will be calculated as (date of interest – date of first dose) + 1.

If the date of interest occurs prior to the date of first dose of study drug, then study day will be calculated as (date of interest – date of first dose/randomization). There is no study day 0

5.5. Coding Dictionaries

Medical history, AEs, and concurrent procedures will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.1. Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary version B3 (September 2021).

6. ANALYSIS POPULATIONS

6.1. Enrolled Population

Enrolled Population includes all participants who signed the informed consent form.

6.2. Safety Population

Safety Population includes all participants who are exposed to any amount of either study drug. This population will be used for analysis of safety data.

6.3. Modified Intent-to-Treat Population

Modified Intent-to-Treat Population (mITT) includes all participants who had at least one full dose of the combined study drugs, had measurable disease at baseline, and had at least one post-baseline assessment. Participants without a post-baseline assessment who discontinued study treatment due clinical progression, death, or a related AE will also be included in the mITT population. Participants without measurable disease at baseline or who do not have the disease of interest in the Dose Expansion phase will be excluded. This population will be used for analysis of efficacy data.

6.4. Pharmacokinetic Population

PK Population includes all participants who received at least 1 dose of rebastinib and had at least 1 non-missing PK concentration in plasma reported for rebastinib. This population will be used for analysis of PK data. Analysis of PK data will be described in a separate document.

7. ANALYSES AND SUMMARIES

7.1. General Considerations

Data collected in this study will be documented using summary tables and participant data listings.

The analyses in this SAP will be used to support an abbreviated CSR that provides a comprehensive summary of safety. Efficacy will be summarized for participants in the Dose Expansion phase only using ORR only. All other efficacy parameters will be listed. Analyses of PK, pharmacodynamic, pharmacogenomic, and PRO data, if conducted, will be described in separate analysis plans.

Continuous variables will be summarized using descriptive statistics (number of participants, mean, median, standard deviation, minimum, and maximum). The mean and median will be reported out to 1 decimal place more than the level of precision of the data being reported, the standard deviation will be reported out to 2 decimal places more than the level of precision of the data being reported, and the minimum and maximum will be reported out the level of precision of the data being reported. Further, a maximum of 4 decimal places will be used for all summary statistics unless otherwise specified.

Categorical variables will be summarized using frequency distributions and proportions. The frequencies distributions and proportions will be presented with 1 decimal place. Proportions, when appropriate, will be reported with exact 2-sided 90% confidence intervals (CIs).

Unless specified, the mITT Population is used for efficacy analysis and the Safety Population is used for the safety analysis.

All data summaries will be descriptive. No statistical testing will be performed.

Statistical analysis will be performed using SAS® (version 9.4 or newer).

7.2. Participant Disposition

Participant disposition will be summarized for all participants in the Enrolled Population by study part, by dose cohort in the Dose Escalation phase, and by expansion cohort in the Dose Expansion phase. The number of participants in the Safety Population, mITT Population, and reasons participants that were removed from the mITT population will be summarized. Reasons for discontinuing study treatment will be summarized separately for rebastinib and carboplatin. The number and proportion of participants who indicated they completed the study, as well as those who discontinue the study will be summarized along with the reason for discontinuation. Follow-up time, which is defined as the time from first dose of study treatment until last contact, will be summarized as a continuous variable.

Primary reason for rebastinib treatment discontinuation includes the following criteria:

- Adverse Event
- Death
- Lost to follow-up
- Non-Compliance with the Drug

- Physician Decision
- Pregnancy
- Clinical Progression
- Radiological Progression
- Termination of Study by Sponsor
- Withdrawal by Patient from Treatment
- Other

Primary reason for carboplatin treatment discontinuation includes the following criteria:

- Adverse Event
- Death
- Lost to Follow-up
- Non-Compliance with the Drug
- Physician Decision
- Pregnancy
- Clinical Progression
- Radiological Progression
- Termination of Study by Sponsor
- Withdrawal by Patient from Treatment
- Other

Primary reason for study discontinuation includes the following criteria:

- Completed
- Death
- Lost to Follow-up
- New Anticancer Therapy
- Withdrawal by Patient from Study
- Termination of Study by the Sponsor
- Other

Participant disposition data will also be presented in data listings.

7.3. Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the clinical protocol.

Protocol deviations will be classified as major or minor by medical review prior to primary analysis. Number and percentage of participants with a major or minor protocol deviation (including categories of deviations) will be tabulated for Safety Population as classified by medical reviewers.

Important protocol deviations will be identified as those deviations from the study protocol that may significantly impact the completeness, accuracy, and/or reliability of the trial data; that may significantly affect a subject's rights, safety, or well-being. Number and percentage of participants with an important protocol deviation (including categories of deviations) will be tabulated for Safety Population.

A listing of all protocol deviations, including protocol deviations related to COVID-19, will also be provided.

7.4. Demographics and Baseline Characteristics

7.4.1. Demographic Characteristics

Demographic and baseline characteristics at study entry will be summarized for the Safety Population by study part.

Demographic and baseline variables to be summarized include:

- Continuous variables
  - Age (years) at time of consent
  - Height (cm) at screening
  - Weight (kg) at screening
  - Body mass index (BMI) (kg/m^2) at screening
- Categorical variables
  - Gender
    - If female, is subject of childbearing potential?
    - If not of childbearing potential, Reason?
  - Race
  - Ethnicity

Demographic characteristics will also be presented in data listings.

7.4.2. Medical History

Medical history will be summarized for the Safety Population by study part. The medical history shall include a complete review of systems, past medical and surgical histories, and any allergies.

The frequency count and percentage of participants experiencing any medical conditions will be tabulated by system organ class (SOC) and PT. If a PT or SOC was reported more than once for a participant, the participant would only be counted once in the incidence for that PT or SOC.

Medical history will also be presented in data listings.

7.4.3. Cancer History

Cancer history data will be summarized for the Safety Population by study part. Cancer history will include:

- Time from initial diagnosis to first dose date (years), calculated as (First dose date – initial diagnosis date)/365.25
- Cancer type
- Stage at initial diagnosis

Cancer history will also be presented in data listings.

7.4.4. Prior Anti-Cancer Therapy and Procedures

Prior anti-cancer therapy and procedures will be summarized for the Safety Population by study part. Prior anti-cancer therapy will include:

- Number of prior anti-cancer treatment regimens
- Type of prior anti-cancer therapy, including chemotherapy, immunotherapy, hormonal therapy, targeted therapy, other
- Prior use of carboplatin and paclitaxel (both individually and in combination)
- Prior anti-cancer surgery
- Prior anti-cancer radiation therapy

The number of prior anti-cancer treatment regimens will be defined as the number of unique regimen numbers provided. Treatment regimens that only include hormonal therapy will not be counted as a treatment regimen. Number of prior treatment regimens will be summarized as both a continuous and categorical variable.

Prior anti-cancer therapies and procedures will also be presented in data listings.

7.4.5. Prior Medications and Procedures

Prior medications and procedures will be summarized for the Safety Population by study part. Prior medications and procedures include any medication or non-drug therapy or procedure not used to treat the participant's cancer taken or performed within 30 days prior to screening and before the first dose of study drug. Prior medications will be coded using the World Health Organization Drug Dictionary. Prior non-drug therapies and procedures will be coded using MedDRA.

The number and proportion of the subjects who took each medication, or had qualifying prior procedures, will be tabulated by the ATC-2 level and preferred name for prior medications. A subject will only be counted once within each ATC-2 code and within each preferred name.

Prior medications and procedures not used to treat the participant's cancer will also be presented in data listings.

7.4.6. Concomitant Medications and Procedures

Concomitant medications and procedures will be summarized for the Safety Population by study part. Concomitant medications and procedures include any medication or non-drug therapy or procedure not used to treat the participant's cancer taken on or after the first day of study drug dose through the 30-Day Safety Follow-up Visit, or initiation of new anti-cancer therapy. Medications

that started before the first dose of study drug and were ongoing on the date of the first dose will be considered concomitant medications. Concomitant medications will be coded using the World Health Organization Drug Dictionary. Concomitant non-drug therapies and procedures will be coded using MedDRA.

The number and proportion of the subjects who took each medication, or had qualifying concomitant procedures, will be tabulated by the ATC-2 level and preferred name for concomitant medications. A participant will only be counted once within each ATC-2 code and within each preferred name.

Concomitant medications and procedures will also be presented in data listings.

7.5. Safety Analysis

Safety data will be summarized for the Safety Population by study part.

7.5.1. Study Drug Exposure

Study drug exposure will be assessed for each of the two study drugs, rebastinib and carboplatin, separately. Study drug exposure will be summarized for the following parameters:

- Duration of treatment (months), calculated as:
  - (Last dose date – first dose date + 1) / 30.4375
- Number of cycles received
- Number of cycles where carboplatin was held or skipped
- Total dose (mg), defined as the sum of the actual doses (mg) administered
- Average daily dose (mg/day) (for rebastinib only), calculated as:
  - Total dose (mg) / duration of treatment (day)
- Average dose per cycle (mg/cycle) (for carboplatin only), calculated as:
  - Total dose (mg) / number of cycles

The duration of the entire treatment regimen will also be summarized and will be calculated as: (Treatment discontinuation date – first dose date + 1) / 30.4375.

Study drug exposure will also be presented in data listings.

7.5.2. Adverse Events

AEs will be coded using MedDRA v24.1 or higher and will be summarized by SOC and PT of MedDRA. Severity of AEs will be assessed by investigators according to CTCAE (v5.0). For incidence summaries, a missing toxicity grade of an AE will be conservatively imputed as severe (Grade 3).

Pre-treatment AEs are those occurring after the participant signed the informed consent and before the administration of the first dose of study treatment.

Treatment-emergent adverse events (TEAEs) are defined as any AEs that occur after administration of the first dose of study drug and through 30 days after the last dose of study

drug, any event that is considered drug-related and occurred after administration of the first dose of study drug, or any event that is present at baseline but worsens in severity or is subsequently considered drug-related by the Investigator.

Drug-related TEAEs are defined as 'related' or 'possibly related' to study drug as assessed by the Investigator. Any AEs with missing relationship to study drug will be considered as related to study drug.

If a participant has multiple occurrences of the same SOC or PT, then only the most severe event will be summarized in the tables for that SOC.

An overall AE summary for number of participants will be presented for the following categories:

- TEAE
- Grade 3/4 TEAE
- Treatment-emergent serious adverse event (SAE)
- TEAE leading to death
- TEAE leading to dose modification of rebastinib (interruption, reduction, or discontinuation)
- TEAE leading to dose interruption of rebastinib
- TEAE leading to dose reduction of rebastinib
- TEAE leading to treatment discontinuation of rebastinib
- Rebastinib-related TEAE
- Rebastinib-related Grade 3/4 TEAE
- Rebastinib-related treatment-emergent SAE
- Rebastinib-related TEAE leading to death
- Rebastinib-related TEAE leading to dose modification of rebastinib (interruption, reduction, or discontinuation)
- Rebastinib-related TEAE leading to dose interruption of rebastinib
- Rebastinib-related TEAE leading to dose reduction of rebastinib
- Rebastinib-related TEAE leading to treatment discontinuation of rebastinib
- AESI
- DLT

The following types of events will be tabulated by SOC and PT. Summaries will be sorted by decreasing frequency of PT within SOC, which is sorted by the internationally agreed order.

- TEAE
- Grade 3/4 TEAE

- Treatment-emergent SAE
- Rebastinib-related TEAE
- Rebastinib-related Grade 3/4 TEAE
- Rebastinib-related treatment-emergent SAE

Summaries of TEAEs by decreasing frequency of PT will be presented for:

- TEAE
- Grade 3/4 TEAE
- Treatment-emergent SAE
- TEAE leading to death
- TEAE leading to dose modification of rebastinib (interruption, reduction, or discontinuation)
- TEAE leading to dose interruption of rebastinib
- TEAE leading to dose reduction of rebastinib
- TEAE leading to treatment discontinuation of rebastinib
- Rebastinib-related TEAE
- Rebastinib-related Grade 3/4 TEAE
- Rebastinib-related treatment-emergent SAE
- Rebastinib-related TEAE leading to death
- Rebastinib-related TEAE leading to dose modification of rebastinib (interruption, reduction, or discontinuation)
- Rebastinib-related TEAE leading to dose interruption of rebastinib
- Rebastinib-related TEAE leading to dose reduction of rebastinib
- Rebastinib-related TEAE leading to treatment discontinuation of rebastinib

Summaries of AESIs by descending frequency of each individual AESI term will be presented.

If a SOC or PT was reported more than once for a participant, the participant would only be counted once in the incidence for that SOC or PT.

The following listings will be provided:

- All AEs (flag TEAE)
- Related TEAEs
- Grade 3/4 TEAEs
- DLTs
- SAEs

- TEAEs leading to study treatment discontinuation (rebastinib or carboplatin)
- TEAEs leading to death
- AESIs

7.5.3. Dose-Limiting Toxicities

A DLT will be defined as any one of the following AEs during the first cycle of treatment occurring during Dose Escalation of the study up until the time of establishing the MTD or an RP2D, unless it is clearly and incontrovertibly due to disease progression or other identifiable extraneous causes.

- Any AE preventing administration of ≥80% of planned doses of rebastinib during the first cycle
- A delay in the initiation of Cycle 2 more than 2 weeks due to a lack of adequate recovery from toxicity
- Hematologic AEs:
  - Grade 4 neutropenia (<500/mm^3; <0.5 x 10^9/L) ≥7 days
  - ≥Grade 3 febrile neutropenia
  - Grade 3 thrombocytopenia, associated with bleeding that requires transfusion therapy
  - Grade 4 thrombocytopenia
- Non-hematologic AEs:
  - Any Grade ≥3 non-hematologic toxicity will be considered a DLT except:
    - Grade 3 nausea or vomiting lasting <7 days
    - Grade 3 diarrhea lasting <7 days
    - Grade 3 fatigue
    - Isolated, asymptomatic Grade 3 abnormalities in chemistry laboratory values that last for ≤7 days. This includes electrolyte abnormalities that respond to medical intervention
  - ALT or AST elevation of >3X ULN with total bilirubin elevation of >2X ULN will be considered as a DLT if absence of initial findings of cholestasis such as alkaline phosphatase elevation of <2X ULN and no other reason can be found to explain simultaneous elevation of ALT or AST and total bilirubin

The frequency and percentage of participants who experience a DLT will be summarized for each dose cohort in the Dose Escalation phase separately. DLTs will not be summarized for the Dose Expansion phase.

7.5.4. Clinical Laboratory Parameters

Clinical laboratory data will be collected at Screening, Cycle 1 Day 1, Cycle 1 Day 8 (±1 day), Day 1 (-3 days) of Cycles 2 and above, and the EOT visit (within 14 days of the decision to stop study drug). Laboratory test results that are abnormal and considered clinically significant must be reported as AEs. Screening laboratory results must be available before the first dose of study drug. All samples must be collected in accordance with acceptable laboratory procedures and graded for toxicity as defined by the NCI CTCAE Version 5.0. In the case of clinically significant Grade 3 or 4 laboratory abnormalities, the laboratory test should be repeated at appropriate intervals until recovery to Grade 0 or 1 and results recorded on the unscheduled CRF.

An abnormal study assessment is considered clinically significant if the participant has one or more of the following:

- Worsening, from baseline, concomitant signs or symptoms related to the abnormal study assessment.
- Further diagnostic testing or medical/surgical intervention is required.
- A change in the dose of study drug, if study drug is withheld, or discontinuation from study drug occurs.

Laboratory test results that are abnormal and considered clinically significant must be reported as AEs. Protocol-specified laboratory parameters are listed in Table 2 below.

Table 2: Safety Laboratory Tests

Serum Chemistry	Hematology	Urinalysis[b]
Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Bicarbonate Blood urea nitrogen Calcium Chloride Creatinine Creatine Phosphokinase Follicle-stimulating hormone[a] Glucose Lactate dehydrogenase Magnesium Phosphorus Potassium Sodium Total and direct bilirubin[c] Total protein	Hemoglobin Hematocrit Platelets Leukocytes Differential (absolute): • Eosinophils • Basophils • Neutrophils • Lymphocytes • Monocytes **Coagulation Studies** Activated partial thromboplastin time Prothrombin time International Normalized Ratio	Urine protein Urine blood Specific gravity Urine ketones Urine glucose

a. This may be required to demonstrate a participant is non-childbearing potential
b. If any result is abnormal, a microscopic analysis must be performed by the local laboratory.
c. Indirect bilirubin should be calculated.

Shift from baseline to the worst post-baseline grade according to NCI-CTCAE v5.0 will be summarized for all applicable laboratory parameters. Frequencies and percentages of any worsening and worsening to Grade 3 or 4 will be presented.

Laboratory parameters will also be presented in data listings.

7.5.5. Vital Signs, Weight, and Height

Vital sign measurements will consist of sitting blood pressure, heart rate, respiratory rate, and body temperature assessed at Screening, Cycle 1 Day 1, Cycle 1 Day 8 (±1 day), Day 1 of Cycles 2 and above, and the EOT visit (within 14 days of the decision to stop study drug). These should be assessed following a 5-minute rest (seated or supine position). Height will only be taken at Screening.

Vital signs and weight will be summarized using continuous descriptive statistics and will be presented by study visit and time point for the actual value and change from baseline.

Vital signs, weight, and height will also be presented in data listings.

7.5.6. ECOG Performance Status

ECOG performance status will be presented in data listings.

7.5.7. Electrocardiograms

Single 12-lead ECGs will be performed at Screening, Cycle 1 Day 1, Day 1 of Cycles 2 and above, and the EOT visit. ECG data will be transmitted to the central ECG diagnostic service and all interval measurements will be reviewed and adjusted using the central ECG core labs

methodology by a trained ECG analyst. The values reported by the central ECG diagnostic service and their reference ranges will be used for data analysis.

Number and percentage of participants with notable ECG values will be summarized according to the following categories:

- QTcF increase from baseline > 30 ms, > 60 ms
- QTcF > 450 ms, > 480 ms, > 500 ms
- QTcB increase from baseline > 30 ms, > 60 ms
- QTcB > 450 ms, > 480 ms, > 500 ms
- HR ≤ 50 bpm and/or decrease from baseline ≥ 20 bpm
- HR ≥ 120 bpm and/or increase from baseline ≥ 20 bpm
- PR ≥ 220 ms and increase from baseline ≥ 20 ms
- QRS ≥ 120 ms

12-lead ECG parameters will also be presented in data listings.

7.5.8. Echocardiogram/Multigated Acquisition Scans

Echocardiogram or MUGA will be performed to obtain left ventricular ejection fraction (LVEF). The assessments will be performed at Screening, Day 1 of Cycle 4, every third cycle thereafter (i.e., Cycles 7, 10, 13, etc.), and the EOT visit. LVEF will be summarized overall and as change from baseline by visit utilizing continuous descriptive statistics.

Echocardiogram or MUGA assessments will also be presented in data listings.

7.5.9. Ophthalmologic Examinations

Ophthalmologic examinations will be performed at Screening, Day 1 of Cycle 4, every third cycle thereafter (i.e., Cycles 7, 10, 13, etc.), and the EOT visit.

Participant level analysis of intraocular pressure will also be performed using the maximum value from the visit. Categories of intraocular pressure will be defined as follows: ≤21 mmHg, >21 mmHg, >21 but ≤30 mmHg, and >30 mmHg. The number and percentage of participants in each category will be summarized at baseline, at each visit, and for the maximum post-baseline value. The number and percentage of participants with an increase from baseline of at least 5 mmHg in either eye will also be summarized.

Ophthalmologic examinations will also be presented in data listings.

7.6. Efficacy Analysis

All efficacy analyses will be performed in the mITT population for the Dose Expansion phase only. Tabular summaries for best overall response and ORR will be presented by the expansion cohort. Response assessments are based on RECIST v1.1 (Eisenhauer, Therasse and Bogaerts) except for participants with pleural mesothelioma, which uses mRECIST (Armato III and Nowak). ORR will be analyzed in the mITT population as the primary analysis. ORR with and without confirmation will be summarized.

Efficacy parameters will also be presented in data listings.

7.6.1. Objective Response Rate

The best response (CR, PR, SD, PD, or not evaluable [NE]) according to RECIST v1.1 (or mRECIST for participants with pleural mesothelioma) will be derived for each participant. Participants with no adequate post-baseline disease assessment who otherwise qualify for the mITT population will have a best response of NE and included as non-responders in the analysis of ORR. Response assessed after disease progression will not be considered in determination of the best overall response. The ORR is calculated as the proportion of participants who have achieved best overall response of CR or PR after the initiation of study treatment. Best overall response and ORR with and without confirmation will be summarized. Confirmed responses are those responses that persist on repeat imaging at least 28 days after the initial response assessment. The derivation for best overall response with confirmation is summarized in the table below.

Table 3: Summary of the Best Overall Response Status when Confirmation of Response is Required

Overall Response at First Time Point	Overall Response at Subsequent Time Point	Best Overall Response with Confirmation
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD or PD	SD provided minimum criteria[b] for SD duration met, otherwise PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR or 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

CR = complete response; PR = partial response; SD = stable disease, PD = progressive disease; NE = not evaluable.
[a] 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 patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best confirmed response is PR.
[b] Minimum criteria for SD duration is 4 weeks (6 weeks for first assessment with a -2 week window).

The ORR with and without confirmation will be summarized as a binary endpoint with exact 2-sided 90% CIs estimated using the Clopper-Pearson method.

The frequency and percentage of participants with a best overall response of CR, PR, SD, PD, or NE with and without confirmation will also be summarized.

7.6.2. Clinical Benefit Rate

The CBR at 6, 12, and 21 weeks, defined as the as proportion of participants with overall response of CR, PR, or SD at 6, 12, and 21 weeks, will be derived for each participant. Per protocol, participants could have a disease assessment 14 days prior to the 6-, 12-, and 21-week

time points and therefore assessments performed within 14 days can be used to define the participant as having clinical benefit at that time point.

Participants with no adequate post-baseline disease assessment who otherwise qualify for the mITT population will be included as non-responders in the analysis of CBR.

CBR at 6, 12, and 21 weeks will be presented in data listings.

7.6.3. Duration of Response

DOR will be summarized for participants with a best overall response of PR or CR and is defined as time from first PR or CR until the earliest documented evidence of PD or death due to any cause, whichever occurs first. Data handling for participants without a PD or death event will follow the rules for PFS outlined in Section 7.6.5. DOR in months will be calculated as: (PFS date – first CR/PR date + 1) / 30.4375.

DOR will be presented in data listings.

7.6.4. Time to Response

Time to response is defined as the time from first dose of study drug until the first assessment demonstrating PR or CR. Time to response will be calculated as: (first CR/PR date – first dose date + 1) / 30.4375.

Time to response will be presented in data listings.

7.6.5. Progression-Free Survival

PFS is defined as the time from first dose of study drug until the earliest documented evidence of PD or death due to any cause, whichever occurs first. Participants without a PD or death event will have their PFS time censored at the last valid disease assessment. PFS in months will be calculated as: (PFS date – first dose date + 1) / 30.4375.

The following describes the detailed data handling for defining PFS:

- All assessments, including scheduled and unscheduled assessments, will be used for this analysis
- Participants not in the mITT population, including those without measurable disease at baseline are excluded
- Participants without a progression or death event will have their PFS time censored on the date of last adequate disease assessment
- Participants who start a new anti-cancer therapy (including surgical resection of the lesions, radiotherapy of the lesions, or a new anti-cancer treatment) prior to an event will have their PFS time censored on the date of last adequate disease assessment prior to the start date of the new anti-cancer therapy
- Participants with an event after 2 or more consecutively missed disease assessments, defined as more than 126 days without a disease assessment (2 9-week assessment intervals) will have their PFS time censored on the date of last adequate disease assessment prior to the missed assessments

- Participants who do not have an adequate post-baseline tumor assessment will be censored on Day 1 unless death occurs on or before the time of the second planned disease assessment (ie, ≤12 weeks after the date of first dose) in which case the death will be considered an event

PFS time in months and whether a participant had a PFS event will be presented in data listings.

7.6.6. Time to Progression

TTP is defined as the time from first dose of study drug until the earliest documented evidence of PD. Participants without a PD event will have their TTP time censored according to the same censoring rules as PFS. Participants who die without a PD event will have their TTP censored at the last valid disease assessment prior to the death. TTP in months will be calculated as: (TTP date – first dose date + 1) / 30.4375.

TTP in months and whether a participant had a progression event will be presented in data listings.

7.6.7. Overall Survival

OS is defined as the time from first dose of study drug until the date of death from any cause. Participants without a death event will have their OS time censored at the last contact date. OS in months will be calculated as: (OS date – first dose date + 1) / 30.4375.

OS time in months and whether a participant had an OS event will be presented in data listings.

7.6.8. CA-125 Response (ovarian cancer expansion cohort only)

CA-125 response is defined as at least 50% reduction in CA-125 levels from baseline. The response must be confirmed and maintained for at least 28 days. Participants in the mITT population with a baseline and two post-baseline assessments will be included in the analysis of CA-125 response. If a participant has a baseline assessment and only one post-baseline assessment, then they will be excluded from the analysis.

CA-125 response will be presented in data listings.

7.7. Patient-Reported Outcomes Analysis

PRO analyses, if conducted, are outside the scope of this SAP.

7.8. Pharmacokinetic Analysis

PK analyses, if conducted, are outside the scope of this SAP.

7.9. Biomarker and Pharmacodynamic Analysis

Biomarker and pharmacodynamic analyses, if conducted, are outside the scope of this SAP.

7.10. Pharmacogenomic Analysis

Pharmacogenomic analyses, if conducted, are outside the scope of this SAP.

8. REFERENCES

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