# Statistical Analysis Plan

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| **Protocol Title:** | A Phase 2, Multicenter, Open-label Study of Sotorasib (AMG 510) in Subjects with Stage IV NSCLC Whose Tumors Harbor a $KRAS^{G12C}$ Mutation in Need of First-line Treatment (CodeBreaK 201) |
| **Short Protocol Title:** | Sotorasib (AMG 510) in Subjects with NSCLC with $KRAS^{G12C}$ Mutation in Need of First-line Treatment |
| **Protocol Number:** | 20190288 |
| **NCT Number:** | NCT04933695 |
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| Version Number | Date (DDMMMYYYY) | Summary of Changes, including rationale for changes |
|---|---|---|
| Original (v1.0) | 16SEP2021 | |
| Amendment 1 (v[2.0]) | 05MAY2022 | 1. Updated as per protocol amendment 4 dated 25FEB2022<br>2. Updated section 9.6.2 Adverse Events.<br>3. Study specific analysis sets added |
| Amendment 2 (v[3.0]) | 27FEB2023 | 1. Section 5 : Removed 'consecutive' word from BOR and OR definitions. For BOR of SD the reference timepoint is changed from 'cycle 1 day 1' to 'baseline'<br>2. Section 6.1.3: Added word 'With' in FAS-local definition for clarity<br>3. Section 9.6.2: Removed TEAE and TRAE summary by SOC, HLT and PT<br>4. Section 9.1: The method for CIs calculation for the median and percentiles is changed from Brookmeyer and Crowley method (1982) to Klein and Moeschberger (1997) with log-log transformation.<br>5. Section 9.4: Added 'History of Bone Metastasis' in baseline disease characteristics<br>6. Section 11: Added reference for method Klein and Moeschberger (1997)<br>7. Section 14: Added a new appendix 'Appendix E Lab Parameters for Analysis' |
| Amendment 3 (v[4.0]) | 09FEB2024 | 1. Section 3.2: Added a rationale for not reaching planned enrollment.<br>2. Section 4.2: Removed subgroup efficacy analysis due to limited sample size.<br>  <br>4. Section 6: 1. Removed central biomarking testing requirement from Full analysis set definitions due to limited evaluable central biomarker results. 2. Removed Investigator full analysis set with central biomarker confirmation (iFAS-central) and full analysis set with/without central |

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|---|---|---|
| | | biomarker confirmation (FAS-local) . 3. Renamed FAS-central as FAS and iFAS-local as iFAS. 4. Removed OS analysis set, iFAS will be used for final analysis of OS. 5. Added following sentence in safety analysis set “This analysis set will be used for safety analyses. Safety analyses will be performed across and by treatment dose arm based on the actual highest dose received at interim analysis and only across treatment dose arms at final analysis”. 6. Removed table 6.1.<br>5. Section 7.2: 5: Updated wording to indicate that primary analysis (PA) will be combined with final analysis (FA) due to early study termination before enrollment is completed.<br>6. Section 9.1: Added details that “Efficacy and safety analyses will be summarized across and by treatment dose arm for interim analysis and across treatment dose arms for final analysis”.<br>7. Section 9.2: updated wording that data cut-off date is not applicable for final analysis.<br>8. Section 9.3: Removed sentence “In addition, a separate listing of all inclusion and exclusion deviations will be provided” as all devitaions related to inclusion and exclusion criteria are considered as IPDs now.<br>9. Section 9: In sub-sections, mentioned that analyses will be performed across treatment dose arms.<br>10. Section 9: Table 9.1 updated to update the analysis sets as per updates in section 6.<br>[redacted]<br>12. Section 9.6.2: Removed high level term from EOI summary.<br>13. Section 9.6.4: Removed Heart rate, respiratory rate and oxygen saturation summaries.<br>14. Section 10: Added changes from protocol specified analyses and rationale. |

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| **Amendment 4 (v[5.0])** | **20JUN2025** | **1. Section 9.5: Added additional timepoints for PFS and OS KM rates.**<br>**2. Section 9.6.2: 1. Updated EOI analysis, 2. Added disease progression related AE listing.**<br>**3. Section 9.6.3: Replaced "suspected" with "potential" for Hy's law cases.**<br>**4. Section 9.6.8: Removed cumulative dose, and the average dose per day summary as the exposure will be presented across treatment groups.**<br>**5. Section 9.6.11: Removed by preferred term summary for anti-cancer therapy.**<br>**6. Section 10: 1. Removed cumulative dose summary from exposure of IP. 2. Anti-cancer therapies will not be summarized by preferred term as anti-cancer therapies are not coded.** |

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## List of Abbreviations

| Abbreviation | Explanation |
|---|---|
| BICR | Blinded Independent Central Review |
| BOR | best overall response |
| CRF | case report form |
| CR | complete response |
| CT | computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DCR | disease control rate |
| DOR | duration of response |
| DRT | Data Review Team |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic case report form |
| EGFR | epidermal growth factor receptor |
| EOT | end of treatment |
| eSAE | electronic Serious Adverse Event |
| IV | Intravenous |
| KRAS | Kirsten rat sarcoma |
| LTFU | Long-term follow-up |
| MRI | magnetic resonance imaging |
| NE | not evaluable |
| NSCLC | non-small cell lung cancer |
| NCT | National Clinical Trials |
| OR | objective response |
| ORR | objective response rate |
| OS | overall survival |
| PD | progressive disease |
| PD-1 | programmed cell death |
| PD-L1 | programmed death-ligand 1 |
| PFS | progression-free survival |
| PO | Orally |
| PR | partial response |
| QD | Daily |
| QRS | Q wave, R wave, and S wave |
| QTcF | QT interval by Fridericia |
| RECIST | Response Evaluation Criteria in Solid Tumors |

| | |
|---|---|
| SD | stable disease |
| SFU | safety follow-up |
| *STK11* | serine/threonine kinase 11 |
| TTR | time to response |

# 1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within Amendment 4 of the protocol for study 20190288, Sotorasib (AMG 510) dated 25 February 2022. The scope of this plan includes the interim analysis, the primary analysis and the final analysis that are planned and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified. Pharmacokinetic and pharmacodynamic and biomarker analyses will be performed by Clinical Pharmacology Modeling and Simulation (CPMS) or biomarker group.

# 2. Objectives, Endpoints and Hypotheses

## 2.1 Objectives and Endpoints/Estimands

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To evaluate the tumor objective response rate (ORR) assessed by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria in subjects who receive sotorasib at either 960 mg daily (QD) or 240 mg QD whose tumors are programmed death-ligand 1 (PD-L1) Tumor Proportion Score (TPS) $<$ 1% and/or harbor a serine/threonine kinase 11 (*STK11*) co-mutation, in a subgroup of subjects with PD-L1 < 1% and in a subgroup of subjects with *STK11* co-mutation. | • Objective response (OR) (OR = complete response [CR] + partial response [PR]), measured by computed tomography (CT) or magnetic resonance imaging (MRI) and assessed per RECIST v1.1 per Blinded Independent Central Review (BICR) |
| **Key Secondary** | |
| • To evaluate other measures of efficacy. | • Disease control (CR + PR + stable disease [SD])<br>• Duration of response (DOR)<br>• Time to response (TTR)<br>• Progression-free survival (PFS)<br>• Overall survival (OS) |
| • To evaluate the safety and tolerability of sotorasib. | • Treatment-emergent adverse events, treatment-related adverse events, and changes in vital signs, electrocardiogram [ECGs], and clinical laboratory tests. |
| • Characterize the pharmacokinetics (PK) of | • PK parameters of sotorasib including, but not limited to, |

| | |
|---|---|
| sotorasib following administration as an oral tablet formulation | maximum plasma concentration ($C_{max}$), time to achieve $C_{max}$ ($t_{max}$), and area under the plasma concentration-time curve (AUC) |

| **Exploratory** |
|---|
| [redacted] |

### 2.2 Hypotheses and/or Estimations

No statistical hypothesis will be tested.

## 3. Study Overview

### 3.1 Study Design

This is an open-label, multicenter phase 2 study to explore the anti-tumor effect of sotorasib monotherapy in subjects with metastatic NSCLC with *KRAS p.G12C* mutation whose tumors express < 1% PD-L1 and/or a *STK11* mutation in need of first line treatment. Approximately 170 subjects across approximately 85 sites globally will be randomized in a 1:1 design for treatment with sotorasib at 960 mg orally (PO) QD or 240 mg orally PO QD, stratified by known presence of *STK11* mutation. Subjects will be treated until disease progression as confirmed by Blinded Independent Central Review (BICR), unacceptable toxicity, withdrawal of informed consent, or death, whichever occurs first. All subjects should have a SFU visit approximately 30 (+ 7) days after the end of the last dosing interval of protocol-required therapies or before any new antitumor treatment is started. Following the SFU visit, all subjects will be followed in clinic or via telephone every 12 weeks (± 2 weeks) starting from the date of the last dose of investigational product for assessment of survival and documentation of anti-cancer treatment until death, withdrawal of consent, or end of study, whichever occurs first. Subjects who discontinue sotorasib for reasons other than radiographic disease progression will have long-term follow-up (LTFU) imaging for disease status until disease progression is documented radiographically per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, initiate a non study cancer treatment, withdrawal of consent, or end of study. In select cases, subjects may continue on treatment following radiologic progression if they continue to demonstrate clinical benefit.

### 3.2 Sample Size

Approximately 170 subjects are planned to be enrolled. Subjects will be randomized at a 1:1 ratio to receive either 960 mg QD or 240 mg QD of monotherapy sotorasib. The sample size is chosen to provide the point estimate of ORR with acceptable precision based on its CI. In the below table provides the CIs for one treatment dose arm (n = 85) and across treatment dose arms (n = 170). This study was early terminated and didn't finish targeted enrollment of 170 subjects.

**Table 3.1. Sample Size Determination**

| Sample Size (n) | 95% Exact CI of the True ORR Given an Observed ORR = 0.40 | 95% Exact CI of the True ORR Given an Observed ORR = 0.50 | Probability (ORR 95% Exact CI Lower Bound > 0.32 Given True ORR = 0.50) |
|---|---|---|---|
| 85 | (0.295, 0.512) | (0.390, 0.610) | 90% |
| 170 | (0.326, 0.478) | (0.422, 0.578) | >99% |

ORR = objective response rate

### 3.3 Adaptive Design

Not applicable for the study.

## 4. Covariates and Subgroups

### 4.1 Planned Covariates

The relationship between covariates and efficacy endpoints may be explored if appropriate.

### 4.2 Subgroups

Subgroup efficacy analysis will not be performed due to limited sample size.

## 5. Definitions

**Baseline:**

For any variable, unless otherwise specified, the baseline is the last non-missing assessment taken prior to the first administration of investigational product. Where baseline measurements are taken on the same day as the study specified treatment and no times are present, it will be assumed that these measurements are taken prior to the study specified treatment being administered.

**Baseline ECG Values:**

The mean of the triplicate ECG results should be calculated for Baseline. If fewer than three triplicate ECG results are available, the mean of available ECG results should be calculated. For all post-baseline ECG, the mean of one triplicate ECG results at the same assessment will be calculated and used in the analysis. When an ECG is missing within a triplicate, all available data will be averaged for that time point.

**Best Overall Response (BOR):**

Best overall response (BOR) for a subject is the best response recorded from the start of the treatment until first disease progression/recurrence per RECIST v1.1. Overall

response assessments occurring after the start of the first subsequent anticancer therapy or post first progression will not be included.
BOR is defined as the best response in the following order: CR, PR, SD, PD, or NE, where CR and PR require confirmation by a repeat scan at least 4 weeks after the first documentation of response. A best overall response of SD requires an on-study imaging of SD or better no earlier than 5 weeks after baseline; otherwise the best overall response will be NE or PD, whichever is applicable.

**Change from Baseline:**
Change from Baseline is the arithmetic difference between a post-Baseline value and Baseline value:
Change (absolute) from Baseline = (Post-baseline Value – Baseline Value)
Change (percent) from Baseline = [(Post-baseline Value – Baseline Value) / Baseline Value] x 100

**Death Date:**
Partial or missing death dates will be imputed as specified in Appendix A prior to derivation of any endpoint that utilizes the date of death.

**Disease Control Rate (DCR):**
DCR is defined as the proportion of subjects with objective response or stable disease per RECIST v1.1.

**Duration of Response (DOR):**
DOR is defined as time from the first documentation of objective response subsequently confirmed until the first documentation of disease progression or death due to any cause, whichever comes first:
DOR in months= (PD / death date - response start date + 1) ×12 / 365.25
DOR will be calculated only for subjects who have achieved objective response.
Subjects will be censored using the same censoring rule for PFS defined in Appendix D.

**Last Known Alive Date:**
Last known alive date captures the latest known alive date from exposure, subject visits, disease response, laboratory assessment, vital sign assessment, survival follow-up alive status, disposition, etc.

If death occurred and death date is complete, then last known alive date = death date – 1 day.

**Investigational Product (IP):**
The term 'investigational product' is used in reference to sotorasib.

**Objective Response as per RECIST 1.1 (OR):**
Objective response is defined as best overall response (BOR) of complete response or partial response, as defined by RECIST 1.1. Confirmation is determined by a repeat assessment no less than 4 weeks from the date of first documented assessment of response. Response assessed by blinded independent central review (BICR) and investigator will be summarized separately.

**Objective Response Rate (ORR):**
ORR is defined as the proportion of subjects with an objective response per RECIST v1.1.

**Overall Survival (OS):**
OS is defined as the time from first dose date until event of death due to any cause through the analysis data cutoff (DCO) date.
OS in months = (Date of death– first dose date + 1) ×12 / 365.25
Subjects still alive will be censored at the last date known to be alive through the DCO date. Data available after the DCO date will not be used to derive overall survival.
If there are deaths reported after the DCO date but prior to data snapshot date, data available after the DCO date may be used to derive overall survival for sensitivity analysis.

**Progression-Free Survival (PFS):**
PFS by BICR is defined as the time from first dose date to disease progression by BICR or death due to any cause (whichever comes first).
PFS in months = (PD / death date - first dose date + 1) ×12 / 365.25
The censoring rules are available in Appendix D.

**Relative Dose Intensity (RDI) of AMG 510:**
RDI of AMG 510 is calculated as actual dose intensity / planned dose intensity.
Actual dose intensity for subjects with non-zero duration of exposure is defined as: cumulative actual dose (mg) / actual duration of exposure (days), where cumulative

actual dose (mg) is the total dose given during the treatment phase and the actual duration of exposure = date of last non-zero dose – date of first non-zero dose + 1. For subjects who did not take IP, the actual dose intensity is 0 mg/day.
The planned dose intensity is 960 mg/day or 240 mg/day based on randomized treatment arm.

**Study Day:**
Post study day 1: study day= (date – first dose date) + 1.
Pre study day 1: study day= (date – first dose date).

**Time to Response (TTR):**
TTR is defined as time from first dose date to the first documentation of PR or CR subsequently confirmed. TTR will be calculated only for subjects who achieve objective response.
TTR in months = (date of first evidence of PR/CR - first dose date+ 1) × 12 / 365.25

**Treatment Emergent Adverse Event (TEAE):**
TEAE are events starting on or after first dose of investigational product as determined by "Did event start before first dose of investigational product" equal to "No" or missing on the Events eCRF and up to and including 30 days after the last dose of investigational product excluding events reported after End of Study date. Adverse events that are directly related to **tumor under study or disease progression of the tumor under study**, **based on manual review** MedDRA preferred terms, will be excluded from analysis of TEAEs with the exception of any IP-related AEs.

**Treatment-Related AE:**
A treatment-related AE is any treatment-emergent AE with the relationship flag on the Events eCRF indicating there is a reasonable possibility that the event may have been caused by investigational medicinal product. In the unlikely event that the relationship is missing, the treatment-emergent event will be considered treatment-related and documented in a footnote of the treatment-related summary.

## 6. Analysis Sets

The following sub-sections describe the analysis sets to be used

### 6.1 Full Analysis Set (FAS)

The Full Analysis Set is defined as all subjects who received at least 1 dose of sotorasib and have one or more measurable lesions at baseline as assessed by BICR using RECIST 1.1. The primary analysis for tumor response per BICR and other efficacy-related endpoints will be performed on Full Analysis Set. The central testing results for KRAS p.G12C, PD-L1 and STK11 will not be required to derive full analysis set for final analysis.

### 6.1.1 Investigator Full Analysis Set (iFAS)

For sensitivity analysis of response-related efficacy endpoints using assessment per Investigator and final analysis of OS, Investigator Full Analysis Set is defined as all subjects who received at least 1 dose of sotorasib. This analysis set will be also used to summarize PFS and OS by treatment dose arms to which they are randomized at the interim analyses.

## 6.2 Safety Analysis Set

The Safety Analysis Set (SAS) is defined as all subjects who are enrolled and received at least 1 dose of sotorasib. This analysis set will be used for safety analyses. Safety analyses will be performed across and by treatment dose arm based on the actual highest dose received at interim analysis and only across treatment dose arms at final analysis**.**

## 6.3 Per Protocol Set(s)

Not applicable for the study.

## 6.4 Health-related Quality-of-Life or Health Economics Analyses Set(s)

Not Applicable for the study

## 6.5 Pharmacokinetic/Pharmacodynamic Analyses Set(s)

The PK Analysis Set is defined as all subjects who have received at least 1 dose of sotorasib and have at least 1 PK sample collected. These subjects will be evaluated for PK analysis unless the number of data points required for analysis is not enough, or significant protocol deviations have affected the data, or if key dosing or sampling information is missing. The PK Analysis Set will be used to conduct the analysis of PK data, unless otherwise specified.

## 6.6 Interim Analyses Set(s)

Interim analyses for specific endpoints will use FAS, or those defined in Section 6.7.

### 6.7 Study-specific Analysis Sets

#### 6.7.1 Investigator ORR Analysis Set (OAS)

The investigator ORR Analysis set is defined as all subjects who received at least 1 dose of sotorasib and have had the opportunity to be followed for at least 7 weeks starting from day 1. Subjects who stopped disease assessments prior to 7 weeks will be included in this analysis set if the data cutoff is at least 7 weeks after their first dose date. This analysis set will be used for interim ORR futility analysis.

## 7. Planned Analyses

### 7.1 Interim Analysis and Early Stopping Guidelines

#### 7.1.1 Interim Analyses

A DRT, internal to Amgen but external to the study team, will monitor the study and perform interim futility analyses to facilitate termination in the event of inadequate efficacy. The futility analyses will occur after approximately 20 and 60 subjects across 2 treatment dose arms become response-evaluable, defined as received at least 1 dose of sotorasib and have had the opportunity to be followed for at least 7 weeks starting from day 1. Subjects who stopped disease assessments prior to 7 weeks will be included in this analysis if the data cutoff is at least 7 weeks after their first dose date. The futility analyses will be based on as-is snapshots using site-assessed disease response. Subjects with unconfirmed PR or CR will be counted as responders for these futility analyses if they are still on study at the time of data cutoff and have potential for future confirmation scan. Further enrollment may be terminated if futility is met. The futility rules will be non-binding and will not require enrollment pause. Safety data will also be reviewed at interim futility DRT meetings.

Futility threshold for all response-evaluable subjects across 2 treatment-dose arms and regardless of biomarker subgroups will be calculated using Bayesian predictive probability approach and it will serve as a guidance to the DRT.

Given the existing observed data during the continuous monitoring stage, the Bayesian predictive probability is obtained by calculating the probability of reaching a Go Criterion should the maximum planned final sample size of 170 subjects be enrolled and evaluated. The Go Criterion will be met if the probability that the true ORR exceeds the benchmark ORR is greater or equal to a high probability:

[redacted]

[redacted]

The decision rule and operating characteristics (ie, cumulative stopping probabilities of futility stopping under hypothetical true ORR) are provided in the below table.

**Table 7.1. Futility Stopping Boundaries and Operating Characteristics**

| Number of Response-Evaluable subjects | Stop for Futility if Observing This Number of Responders | Cumulative Probability of Futility Stopping Under Hypothetical True ORR |
|---|---|---|
| [redacted] | | |

ORR = objective response rate

### 7.2 Primary Analysis

The primary analysis is initially planned approximately 6 months after all subjects are enrolled. Due to early study termination before enrollment is completed, the primary analysis will be combined with final analysis. The data will be analyzed once they have been entered, cleaned, and locked.

### 7.3 Final Analysis

The final analysis will occur when the end of study as described in protocol Section has been reached. The data will be analyzed once they have been entered, cleaned, and locked. The purpose of this analysis is to summarize efficacy and safety after all subjects have complete follow-up.

## 8. Data Screening and Acceptance

### 8.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses.

### 8.2 Data Handling and Electronic Transfer of Data

The Amgen Global Study Operations-Data Management (GSO-DM) department will provide all data to be used in the planned analyses. This study will use the RAVE database. The database will be subject to edit checks outlined in the Clinical Data Management Plan (DMP). See details of this section in the DMP.

### 8.3 Handling of Missing and Incomplete Data

Incomplete adverse event and concomitant medication dates missing data will be imputed as described in Appendix A.

### 8.4 Detection of Bias

Lack of protocol compliance and the potential for biased statistical analyses will be examined by assessing the incidence of important protocol deviations in each cohort. The clinical study team will identify and document the criteria for important protocol deviations.

### 8.5 Outliers

PK concentration data will be evaluated for outliers by visual inspection, and decisions to re-assay individual samples will be made in accordance with standard PK evaluation practice.

### 8.6 Distributional Characteristics

Where appropriate, the assumptions underlying the proposed statistical methodologies will be assessed. If required, data transformations of analyses will be utilized.

### 8.7 Validation of Statistical Analyses

Programs will be developed and maintained and output will be verified in accordance with current risk-based quality control procedures.

Tables, figures, and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software; for example, the SAS System version 9.4 or later.

## 9. Statistical Methods of Analysis

### 9.1 General Considerations

Descriptive statistics will be provided for selected demographics, safety & efficacy. Descriptive statistics on continuous data will include means, medians, standard

deviations, and ranges, while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may also be presented. Confidence intervals for proportions will be estimated using an exact method proposed by Clopper-Pearson (Clopper and Pearson, 1934). Kaplan-Meier methods will be used to estimate the median and percentiles for time to event endpoints with CI calculated using the Klein and Moeschberger (Klein and Moeschberger 1997) method with log-log transformation. Kaplan-Meier methods will be used to estimate landmarks for time to event endpoints (eg, 1-year OS) with the Greenwood formula (Kalbfleisch and Prentice, 1980) used to estimate the standard error used in CI calculation.

The analysis of all efficacy endpoints except for OS will be conducted using the Full Analysis Set, unless otherwise specified. The analysis of OS will be conducted using investigator full analysis set**.** Interim futility analyses based on objective response will be conducted in the Investigator ORR Analysis Set. Efficacy and safety analyses will be summarized across and by treatment dose arm for interim analysis and across treatment dose arms for final analysis.

### 9.2 Subject Accountability

The number and percent of subjects who were randomized, received investigational product, discontinued from investigational product (including reasons for discontinuing), completed study, discontinued the study (including reasons for discontinuing) will be summarized. Key study dates for the first subject enrolled, last subject enrolled, last subject's end of study and data cut-off date (not applicable for final analysis) will be presented.

### 9.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's initial visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, subcategory codes, and descriptions will be used during the study. The final IPD list is used to produce the Summary of IPDs table and the List of Subjects with IPDs.

### 9.4 Demographic and Baseline Characteristics

Demographic and baseline disease characteristics will be summarized across treatment dose arms using descriptive statistics for the Full Analysis Set.

These include, but not limited to the following:

- Baseline demographics and characteristics:
  - Age at randomization

  - As continuous variable
  - As categorical variable: (< 65 vs >= 65)
  - Age categories (18 - 64 years, 65 - 74 years, 75 - 84 years, ≥ 85 years)
- Sex (Male, Female)
- Race
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Weight (kg)
- Height (cm)
- Region (North America, Europe, Asia Pacific, Other)

- Baseline disease characteristics:
  - ECOG Performance Status (0, 1)
  - History of Liver Metastasis (Yes, No)
  - History of Bone Metastasis (Yes, No)
  - History of Brain Metastasis (Yes, No)
  - Smoking History (Yes, No)
  - Histology (Squamous, Non-squamous)
  - Time from Initial Diagnosis to Randomization

## 9.5 Efficacy Analyses

**Table 9.1. Efficacy Endpoint Summary Table**

| Endpoint | Primary Summary and Analysis Method | Analysis Set |
|---|---|---|
| **Primary Endpoint** | | |
| ORR | The percentage of subjects with an OR will be summarized along with a 2-sided 95% exact CI based on Clopper-Pearson method. Subjects without a post-baseline tumor assessment will be considered non-responders. | Interim: OAS<br>Primary/Final: FAS<br>Sensitivity analysis using tumor assessments per investigator may be performed to evaluate ORR for subjects in iFAS. |
| **Secondary Endpoints** | | |
| DOR | Kaplan-Meier quartiles and rates for selected durations (eg, > 3, > 6, > 9, > 12 months) | Interim: OAS<br>Primary/Final: FAS |
| DCR | The percentage of subjects with CR, PR and SD will be summarized along with a 2-sided 95% exact CI based on Clopper-Pearson method. Subjects without a post-baseline tumor assessment will be considered non-responders. | Interim: OAS<br>Primary/Final: FAS |

| Endpoint | Primary Summary and Analysis Method | Analysis Set |
|---|---|---|
| **Primary Endpoint** | | |
| ORR | The percentage of subjects with an OR will be summarized along with a 2-sided 95% exact CI based on Clopper-Pearson method. Subjects without a post-baseline tumor assessment will be considered non-responders. | Interim: OAS<br>Primary/Final: FAS<br>Sensitivity analysis using tumor assessments per investigator may be performed to evaluate ORR for subjects in iFAS. |
| TTR | Summary of non-missing sample size (n), mean, standard deviation, median, minimum, and maximum for responders | Interim: OAS<br>Primary/Final: FAS |
| PFS | Kaplan-Meier curves, quartiles, and rates for select timepoints (eg, **3,** 6, **9,** 12, **18** and **24** months) | Interim: iFAS<br>Primary/Final: FAS<br>Sensitivity analysis using tumor assessments per investigator may be performed for subjects in iFAS |
| OS | Kaplan-Meier curves, quartiles, and rates for select timepoints (eg, **3**, 6, **9**, 12, **18** and **24** months) | Interim: iFAS<br>Primary/Final: iFAS |

### 9.5.1 Analyses of Primary Efficacy Endpoint(s)/Estimand(s)

The number and percentage of subjects with a best overall response of Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD), Not Evaluable (NE) will be presented. ORR will be summarized along with a Clopper-Pearson exact 2-sided 95% exact confidence interval (Clopper and Pearson, 1934). Subjects without a post-baseline tumor assessment will be considered non-responders.

### 9.5.2 Analyses of Secondary Efficacy Endpoint(s)

DOR will be calculated only for subjects who achieve a best overall response of PR or better. Subjects will be censored following the censoring strategy described in the definition of PFS time in Appendix D. The distribution of DOR, including the median and quartiles will be characterized using the Kaplan-Meier(KM) method based on the subjects who achieve a best response of PR or CR. The 95% CIs for the median and quartiles of PFS will be constructed using the method of Klein and Moeschberger (1997) with log-log transformation. The rates for select durations (eg, > 3, > 6, > 9, > 12

months) will be reported. The 95% CIs for PFS rates will be estimated using the methods by Kalbfleisch and Prentice (1980) with log-log transformation.
KM curve will be done for DOR if at least 10 subjects have a CR/PR.
The proportion of subjects with disease control (CR, PR or SD) with corresponding exact 2-sided 95% exact CI will be calculated using the Clopper-Pearson method.
The distribution of PFS, including median, will be estimated using the Kaplan-Meier method. PFS rate at the selected time points (e.g. **3**, 6, **9,** 12, **18** and **24** months) will be reported. The 95% CIs for the median and other percentiles of PFS will be constructed using the method of Klein and Moeschberger (1997) with log-log transformation. The 95% CIs for PFS rates will be estimated using the methods by Kalbfleisch and Prentice (1980) with log-log transformation.
OS will be analyzed using the same method as described for the PFS endpoints.
For OS the censoring is up to data cutoff date, If there are deaths reported after the DCO date but prior to data snapshot date, data available after the DCO date may be used to derive overall survival for sensitivity analysis. Time to response will be summarized with the non-missing sample size (n), mean, standard deviation, median, minimum, and maximum for responders, ie, subjects who achieve best overall response of CR, or PR.

### 9.5.3 Analyses of Exploratory Efficacy Endpoint(s)

[redacted]

## 9.6 Safety Analyses

### 9.6.1 Analyses of Primary Safety Endpoint(s)

Unless otherwise specified, statistical analyses on safety endpoint will be done using subjects from the Safety Analysis Set.

### 9.6.2 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 28.0 or later will be used to code all adverse events to a system organ class and a preferred term. The severity of each adverse event will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 criteria.
The subject incidence of all treatment-emergent adverse events (TEAEs), grade 3 or higher TEAEs, serious TEAEs, TEAEs leading to discontinuation of investigational product, TEAEs leading to dose reduction/ interruption of investigational product and, fatal TEAEs will be tabulated overall and by a combination of system organ class (SOC) in alphabetical order, preferred term (PT) in order of descending frequency, and grade.

Subject incidence of all treatment-related adverse events (TRAEs), grade 3 or higher TRAEs, serious TRAEs, TRAEs leading to discontinuation of investigational product, TRAEs leading to dose dose reduction/ interruption of investigational product, and fatal TRAEs will be tabulated overall and by a combination of SOC in alphabetical order, PT in order of descending frequency, and grade.

Subject incidence of adverse events of interest (EOI) (standardized MedDRA queries and/or Amgen Medical Queries), grade 3 or higher EOI, serious EOI, EOI leading to discontinuation of IP, EOI leading to dose reduction/interruption of IP and fatal EOI will be tabulated by EOI category in alphabetical order and PT in order of descending frequency.

In addition, time to first onset of EOI and time to first grade 3 or higher event will be summarized for subjects with an event (days) using descriptive statistics for continuous variable. Duration of EOI and grade 3 or higher events (time of first EOI start till AE end date with AE outcome as resolved) will be summarized using descriptive statistics. Number of subjects and unresolved events will be tabulated.

**Duration of EOI at event level will be summarized for fully resolved event based on episode. If time interval between two consecutive AE data logs for the particular EOI are within 24 hours, they will be collapsed as one episode. Number of episodes per subject will also be summarized.**

A summary of the number of deaths and the cause of death, classified by deaths within 30 days of last dose of study drug and deaths more than 30 days after the last dose, will be provided.

All on study deaths will be listed. **A listing of all TEAE with preferred terms directly related to the tumor under study or disease progression of the tumor under study will be produced.**

### 9.6.3 Laboratory Test Results

Laboratory data will be summarized using descriptive statistics at each scheduled time point across treatment dose arms in the study. For continuous parameters, a summary of the changes from baseline to each post baseline laboratory assessment will also be produced. For the summary of changes from baseline values, subjects without baseline and/or post-baseline value will be excluded.

Shifts in selected laboratory parameters between baseline and the worst on-study value will be summarized according to the NCI CTCAE toxicity grades. Tables of shifts from baseline to the worst-case on-study increased and decreased values (graded according to the NCI Common Toxicity Grading Criteria) will be provided for selected laboratory

parameters with available NCI-CTCAE grades. Unscheduled assessments will be included in the shift tables.

See Appendix E for selected laboratory parameters.

Subject incidence of **potential** Hy's law cases (Hy's law predicts potential for drug-related hepatotoxicity) will be summarized.

A listing of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and total bilirubin values at each time point will be produced for the subjects **potential** of Hy's law case.

#### 9.6.4 Vital Signs

Vital signs including systolic/diastolic blood pressure and body temperature will be summarized by changes from baseline values across treatment dose arm using descriptive statistics. For the summary of changes from baseline by visit, subjects without a baseline and/or post baseline value will be excluded.

#### 9.6.5 Physical Measurements

The analyses of physical measurements will include summary statistics at baseline.

#### 9.6.6 Electrocardiogram

Summaries over time and/or changes from baseline over time will be provided for all ECG parameters across treatment dose arms.

Subjects' maximum change from baseline in QT interval corrected by Fridericia's formula will be categorized and the number and percentage of subjects across treatment dose arms will be summarized. Unscheduled assessments will be included in the determination of the maximum change. The categories are <= 30 msec, > 30 – 60 msec, > 60 msec.

Subjects' maximum post baseline values will also be categorized and the number and percentage of subjects across treatment dose arms will be summarized. The categories are <= 450 msec, > 450 – 480 msec, > 480 – 500 msec, > 500 msec.

#### 9.6.7 Antibody Formation

Not applicable for the study.

#### 9.6.8 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to investigational product (IP) across treatment dose arms. The number of cycles administered will be summarized with an additional breakdown of the number of cycles started. In addition, the duration of therapy and relative dose intensity will be summarized. The number and percent of

subjects with dose modifications and reason for modification will be summarized across treatment dose arms.

#### 9.6.9 Exposure to Non-investigational Product

Not applicable for the study.

#### 9.6.10 Exposure to Other Protocol-required Therapy

Not applicable for the study.

#### 9.6.11 Exposure to Concomitant Medication

Number and proportion of subjects receiving concomitant medication will be summarized by preferred term across treatment dose arms as coded by the World Health Organization Drug (WHO DRUG) dictionary. In addition, the number and proportion of subjects receiving anti-cancer therapies while on study will be summarized across treatment dose arms in the Safety Analysis Set.

### 9.7 Other Analyses

Other analyses in the study include analyses for PK and [redacted] endpoints, which may be specified in the separate analysis plans.

#### 9.7.1 Analyses of Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Endpoints

Nominal sampling times will be used for individual concentration-time plots and tables. Actual dose administered, and actual sampling times will be used for the calculation of PK parameters for each subject. The reasons for excluding any sample from the analyses will be provided.

Individual concentration-time data will be tabulated and presented graphically. Summary of PK concentration over time and PK parameters will be provided. Mean concentration-time profiles for each dose will be provided.

PK parameters will include, but are not limited to, maximum observed concentration ($C_{max}$), time to maximum concentration ($t_{max}$) and area under the plasma concentration-time curve (AUC). Other PK parameters such as AUC from time 0 to the time extrapolated to infinity ($AUC_{inf}$), apparent clearance (CL/F), and terminal half-life ($t_{1/2}$) may be analyzed.

For sotorasib, pharmacokinetic parameters will be determined from the time concentration profile using standard non-compartmental approaches based on the PK Analysis Set. PK parameters will be summarized using descriptive statistics including, but not limited to means, standard deviations, medians, minimums, and maximums.

Based on the review of the data, analyses to describe the relationship between AMG 510 exposure and either pharmacodynamic effect and/or clinical outcome may also be performed.

If performed, details regarding objectives, data handling, and methodology pertaining to any modeling activities will be provided in a separate population modeling analysis plan and/or a separate exposure-response analysis plan.

### 9.7.2 Analyses of Clinical Outcome Assessments

Not applicable for the study.

### 9.7.3 Analyses of Health Economic Endpoints

Not applicable for the study.

### 9.7.4 Analyses of [redacted]

Details will be described in the supplemental statistical analysis plan.

## 10. Changes From Protocol-specified Analyses

This study was early terminated without completing target enrollment of 170 subjects. Due to the reduced sample size and limited evaluable central biomarker results, the result of biomarker subgroup analyses cannot be reliably interpreted. Therefore, we amended efficacy analysis sets to no longer require central biomarker testing results as the inclusion criteria. In addition, considering this study was not intended to compare treatment doses, which would repeat the dose comparison study, and the reduced sample size, all efficacy and safety analyses will be performed across treatment dose arms at final analysis.

The above rationale resulted in the following changes from protocol:

1. Subgroup efficacy analysis will not be performed.
2. The central testing results for KRAS p.G12C, PD-L1 and STK11 will not be required to derive full analysis set for final analysis.
3. Final analysis of OS will be performed on investigator full analysis set instead of OS analysis set which required central testing results for KRAS p.G12C, PD-L1 and STK11.
4. All analyses will be performed across treatment arms instead of by treatment arms for final analysis.
5. Primary analysis (PA) will be combined with final analysis (FA) due to early study termination before enrollment is completed. In the previous SAP amendment, it is already indicated PA and FA may be combined.

6. **Cumulative dose will not be given in exposure to IP as the summary will be presented across treatment arms.**
7. **Anti-cancer therapies will not be summarized by preferred term as anti-cancer therapies are not coded.**

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## 12. Prioritization of Analyses

Not applicable

## 13. Data Not Covered by This Plan

Pharmacokinetic, pharmacodynamic, exposure-response and biomarker analyses will be performed by Clinical Pharmacology Modeling and Simulation (CPMS) or biomarker group.

## 14. Appendices

## Appendix A. Imputation Rules

Below imputation rules will be used to impute start date and stop date of AE, Concomitant Medication. Date of prior anti-cancer therapy, PD-1, PD-L1 and metastasis will be imputed using the same rule when only the date is missing (no imputation when month or year is missing).

**Imputation Rules for Partial or Missing Start Dates**

The reference date for the following rules is the date of first dose of sotorasib.

| | | **Stop Date** | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | **Complete:** ***yyyymmdd*** | | **Partial:** ***yyyymm*** | | **Partial:** ***yyyy*** | | **Missing** |
| **Start Date** | | **< 1st dose** | **≥ 1st dose** | **< 1st dose** ***yyyymm*** | **≥ 1st dose** ***yyyymm*** | **< 1st dose** ***yyyy*** | **≥ 1st dose** ***yyyy*** | |
| **Partial:** ***yyyymm*** | **= 1st dose** ***yyyymm*** | 2 | 1 | n/a | 1 | n/a | 1 | 1 |
| | **≠ 1st dose** ***yyyymm*** | | 2 | 2 | 2 | 2 | 2 | 2 |
| **Partial:** ***yyyy*** | **= 1st dose** ***yyyy*** | 3 | 1 | 3 | 1 | n/a | 1 | 1 |
| | **≠ 1st dose** ***yyyy*** | | 3 | | 3 | 3 | 3 | 3 |
| **Missing** | | 4 | 1 | 4 | 1 | 4 | 1 | 1 |

1=Impute the date of first dose; 2=Impute the first of the month; 3=Impute January 1 of the year; 4=Impute January 1 of the stop year

Note: For subjects who were never treated (first dose date is missing), partial start dates will be set to the first day of the partial month or first day of year if month is also missing.

Imputation Rules for Partial or Missing Stop Dates

Initial imputation

- If the month and year are present, impute the last day of that month.
- If only the year is present, impute December 31 of that year.
- If the stop date is entirely missing, assume the event or medication is ongoing.

If the imputed stop date is before the start date, set stop date to missing.

If the imputed stop date is after the death date, impute as death date.

Imputation Rules for Partial or Missing Death Dates

If death year and month are available but day is missing:

- If yyyymm for the date last known to be alive equals yyyymm for death date, set death date to the day after the date last known to be alive.
- If yyyymm for the date last known to be alive is less than the yyyymm for death date, set death date to the first day of the death month.
- If yyyymm for the date last known to be alive is greater than yyyymm for death date, assume date last known to be alive is in error, set death date to the first day of the death month.

If month and day are missing and year of death is known:

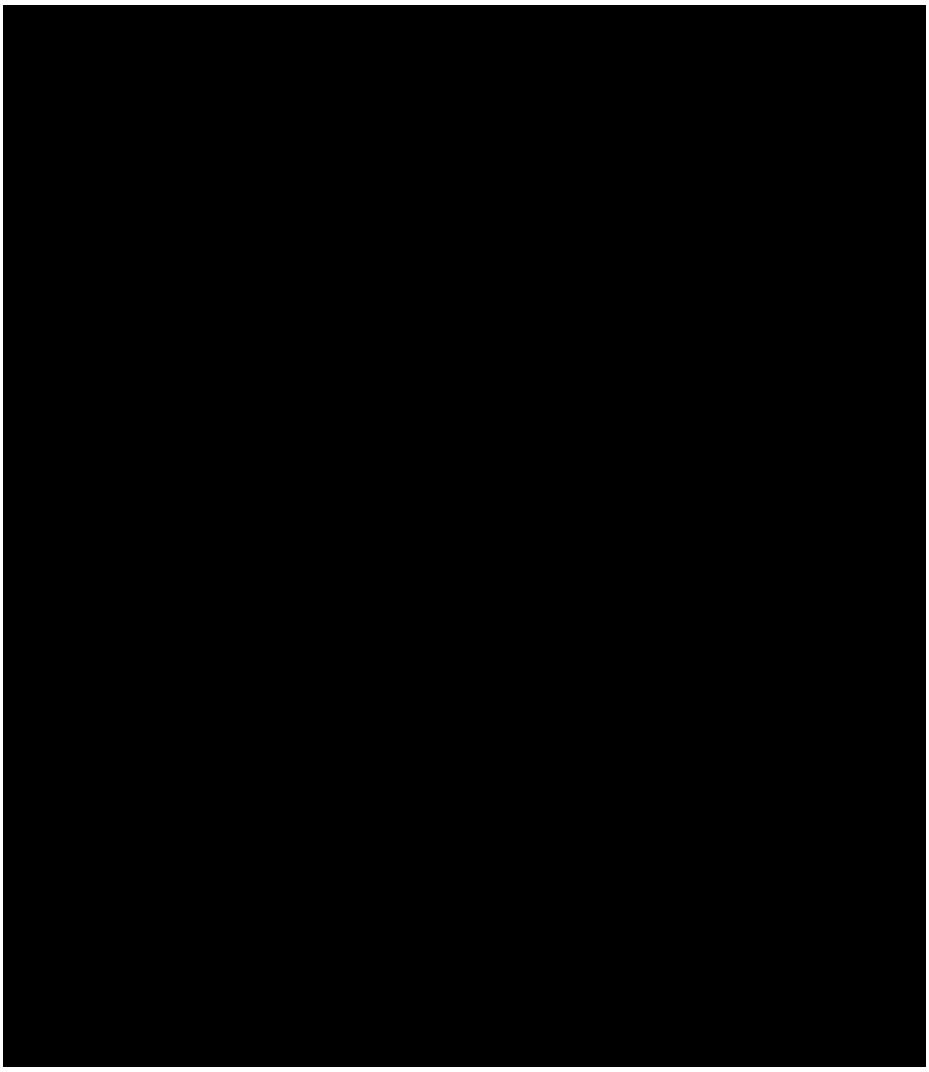
- If yyyy for the date last known to be alive equals yyyy for death date, set death date to the day after last known to be alive date.
- If yyyy for the date last known to be alive is less than yyyy for death date, set death date to the first day of the death year.
- If yyyy for the date last known to be alive is greater than yyyy for death date, assume date last known to be alive is in error, set death date to the first day of the death year.

If a death date is totally missing:

Do not impute and censor the subject survival time.

## Appendix B. Code Fragments

Provisional Code Fragments for calculating a confidence interval using the Clopper Pearson Method. The following example SAS code will be utilized as reference for the response rate analysis providing the proportion of subjects responding to treatment with corresponding 95% confidence intervals.



## Appendix C. BOR Calculation Algorithm

BOR by investigator will need to be derived based on timepoint response collected on RECIST 1.1 CRF. Table 2 provides the BOR determination per RECIST 1.1 for trials where response confirmation is required. A BOR determined by Table 2 is considered a *Confirmed_BOR*.

At interim analysis, an unconfirmed response rate may be reported in addition to the confirmed response rate. The unconfirmed rate includes subjects who achieved a PR or CR and are awaiting a confirmative scan (ie, unconfirmed responders). If these subjects have disease progression or death before the confirmative scan, then they are no longer considered as unconfirmed responder awaiting confirmative scan. *Interim_BOR* is defined to include these subjects in addition to *Confirmed_BOR*. Table 3 outlines the steps to derive *Confirmed_BOR* and *Interim_BOR* given the timepoint assessments.

**Table 2. BOR per RECIST 1.1**

| Criterion | Timepoint T1 Response | T1 ≥ 35* days after baseline? | Timepoint T2 Response | T2 ≥ 35* days after baseline? | T2 ≥ 28 days after T1? | BOR |
|---|---|---|---|---|---|---|
| C1 | CR | Yes | CR | - | Yes | CR |
| C2 | | | CR | - | No | SD |
| C3 | | | PR, SD | - | - | Query data** |
| C4 | | | PD | - | - | SD |
| C5 | | | NE, No further evaluations | | | SD |
| C6 | | No | CR | - | Yes | CR |
| C7 | | | CR | Yes | No | SD |
| C8 | | | PR, SD | - | - | Query data** |
| C9 | | | PD | - | - | PD |
| C10 | | | NE, No further evaluations | | | NE |
| C11 | PR | Yes | CR, PR | - | Yes | PR |
| C12 | | | CR, PR | - | No | SD |
| C13 | | | SD | - | - | SD |
| C14 | | | PD | - | - | SD |
| C15 | | | NE, No further evaluations | | | SD |
| C16 | | No | CR, PR | - | Yes | PR |
| C17 | | | CR, PR | Yes | No | SD |
| C18 | | | SD | Yes | - | SD |
| C19 | | | PD | - | - | PD |
| C20 | | | NE, No further evaluations | | | NE |
| C21 | SD | Yes | CR, PR, SD, PD, NE, no more evaluation | | | SD |
| C22 | | No | CR, PR, SD | Yes | - | SD |
| C23 | | | CR, PR, SD | No | - | NE |
| C24 | | | PD | - | - | PD |
| C25 | | | NE, No further evaluations | | | NE |
| C26 | PD | | - | | | PD |
| C27 | NE | - | NE, No further evaluations | | | NE |
| C28 | | - | CR, PR, SD | Yes | - | SD |
| C29 | | - | CR, PR, SD | No | - | NE |
| C30 | | - | PD | - | - | PD |

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable.

* CR and PR will need at least 4 weeks confirmation; SD will need at least 6 weeks confirmation. The threshold of 35 days accounts for the earliest available assessment by RECIST v1.1, as for the tumor assessment per SOA: *Imaging will be performed every 6 weeks from cycle 1 day 1 (± 7 days)*.

** 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 response is PR.

**Table 3. BOR Derivation Step for GSP**

<table>
<tr><th colspan="2">Step 1. Derive Confirmed_BOR at each visit</th></tr>
<tr><td colspan="2">Derive Confirmed_BOR at each visit:<br>i) At Visit 1: Using the Visit 1 scan result and refer to Table 2 to derive Confirmed_BOR.<br>ii) At Visit 2 onward:<br>(a) If current visit is CR or PR: Find last scan that is not NE or SD and at least 28 days before current visit. Derive BOR_temp as below:
<table>
<tr><th>Last scan</th><th>Current</th><th>BOR_temp</th></tr>
<tr><td>CR</td><td>CR</td><td>CR</td></tr>
<tr><td>PR</td><td>CR</td><td>PR</td></tr>
<tr><td>PR</td><td>PR</td><td>PR</td></tr>
</table>
(b) If none of above fits, find last scan that is not NE, reference Table 2 to derive BOR_temp.<br>iii) Current visit Confirmed_BOR = best of (BOR_temp, last visit confirmed_BOR). Use rule CR > PR > SD > PD > NE</td></tr>
<tr><th colspan="2">Step 2. Derive Interim_BOR at last visit prior to DCO</th></tr>
<tr><td>For subjects who discontinue tumor assessment (ie, had PD, death, next therapy, withdraw consent, or end of study):<br><br>Assign Interim_BOR = Confirmed_BOR</td><td>For subjects with potential for more assessment (ie, no PD, death, next therapy, withdraw consent, or end of study), unconfirmed PR/CR can be considered responders.<br><br>• If any scan is CR and no PD/death, then Interim_BOR = CR.<br>• If any scan is PR and no CR or PD/death, then Interim_BOR = PR.<br>• Else, Interim_BOR = Confirmed_BOR at the latest scan.</td></tr>
</table>

## Appendix D. PFS Calculation and Censoring Rule

The following tables consider 3 different kind of disease progression: (1) “PD per BICR” refers to RECIST 1.1 PD from radiographic scans and read by Central Review, (2) “PD per investigator” refers to RECIST 1.1 PD from radiographic scans and read by investigator, (3) “clinical progression” refers to investigator’s judgement based on patients’ symptoms.

### Table D.1. Primary analysis: PFS Based on Central Review

| Situation up to DCO/EOS | Date of Event or Censor | Outcome |
|---|---|---|
| No evaluable post-baseline tumor assessments per BICR, no death recorded | First dose date | Censor |
| PD per BICR | First detection of PD per BICR | Event |
| No PD per BICR, but death recorded | Date of death | Event |
| Start of new anti-cancer therapy prior to any PD per BICR or death | Date of last evaluable assessment per BICR before or on start of new anti-cancer therapy | Censor |
| No PD per BICR, no death recorded, no start of new anti-cancer therapy | Date of last evaluable assessment per BICR | Censor |
| Death or PD per BICR immediately after consecutively missed more than one tumor assessment | Date of last evaluable assessment per BICR with documented non-progression prior to missing assessment(s) [a] | Censor |

DCO = Data Cutoff; EOS = End of Study; PD = Progressive disease

[a] This supersedes the previous rules that result in PFS event at date of PD or death.

**Table D.2. Sensitivity Analysis 1: PFS Based on Investigator Assessments**

| Situation up to DCO/EOS | Date of Event or Censor | Outcome |
|---|---|---|
| No evaluable post-baseline tumor assessments per investigator assessments, no death recorded | First dose date | Censor |
| PD per investigator assessments | First detection of PD per investigator assessments | Event |
| No PD per investigator assessments, but death recorded | Date of death | Event |
| Start of new anti-cancer therapy prior to any PD per investigator assessments or death | Date of last evaluable tumor assessment per investigator assessments before or on start of new anti-cancer therapy | Censor |
| No PD per investigator assessments, no death recorded, no start of new anti-cancer therapy | Date of last evaluable tumor assessment per investigator assessments | Censor |
| Death or PD per investigator assessments immediately after consecutively missed more than one tumor assessment | Date of last evaluable tumor assessment per investigator assessments with documented non-progression prior to missing assessment(s) [a] | Censor |

DCO = Data Cutoff; EOS = End of Study; PD = Progressive disease

[a] This supersedes the previous rules that result in PFS event at date of PD or death.

**Table D.3. Sensitivity Analysis 2: PFS Based on Investigator and Consider Clinical Progression as Events**

| Situation up to DCO/EOS | Date of Event or Censor | Outcome |
|---|---|---|
| No evaluable post-baseline tumor assessments per investigator assessments, no death recorded | First dose date | Censor |
| Clinical progression or PD per investigator assessments | First detection of clinical progression or PD per investigator assessments | Event |

| | | |
|---|---|---|
| i.e. progressions documented on EOIP or end of radiographic follow-up CRF form whichever is earlier | | |
| No clinical progression or PD per investigator assessments, but death recorded | Date of death | Event |
| Start of new anti-cancer therapy prior to any PD (per investigator assessment, or clinical progression) or death | Date of last evaluable assessment per investigator assessments before or on start of new anti-cancer therapy | Censor |
| No PD per investigator assessments, no clinical progression, no death recorded, no start of new anti-cancer therapy | Date of last evaluable assessment per investigator assessments | Censor |
| Death or PD per investigator assessments or clinical progression immediately after consecutively missed more than one tumor assessment | Date of last evaluable assessment per investigator with documented non-progression prior to missing assessment(s) [a] | Censor |

DCO = Data Cutoff; EOIP = End of Investigational Product**;** EOS = End of Study; PD = Progressive disease
[a] This supersedes the previous rules that result in PFS event at date of PD or death.

## Appendix E. Lab Parameters for Analysis

| Local Laboratory | | | |
|---|---|---|---|
| Chemistry | Hematology | Urinalysis | Lab parameters for shift tables |
| Sodium<br>Potassium<br>Chloride<br>Bicarbonate (HCO3)<br>Total protein<br>Albumin<br>Calcium<br>Magnesium<br>Phosphorus<br>Glucose<br>Blood urea nitrogen (BUN)[a]<br>Urea[a]<br>Creatinine<br>Total bilirubin<br>ALP<br>ALT<br>AST<br>TSH<br>Total Triiodothyronine (T3)<br>Free Triiodothyronine (T3)<br>Free Thyroxine (T4)<br>Total cholesterol<br>HDL Cholesterol<br>LDL Cholesterol<br>Triglyceridese<br>Calcium corrected (derived)<br>Glomerular Filtration Rate (derived) | Hemoglobin<br>Hematocrit<br>Platelets<br>RBC<br>Total white blood cell count (WBC)<br>• White blood cell differential<br>• Total neutrophils (or segmented neutrophils and bands/stabs)<br>• Eosinophils<br>• Basophils<br>• Lymphocytes<br>• Monocytes | Protein | Albumin<br>ALP*<br>Total bilirubin*<br>Calcium corrected<br>Creatinine*<br>Glucose<br>Hemoglobin*<br>Potassium<br>Magnesium<br>Sodium<br>Platelets<br>AST*<br>ALT* |

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; HDL = high density lipoprotein; LDL = low density lipoprotein; WBC = white blood cell; TSH = thyroid stimulating hormone; WBC = white blood cell coun

* For parameters where grade depends on baseline value, tables based on worst post baseline grade will be presented.

[a] Urea will be converted to BUN to present in lab summary as below if standard unit for BUN is collected as mg/dL. If both Urea and BUN are in mmol/L then no conversion will be done:
Urea (mmol/L) divided by 0.357 = BUN (mg/dL)