Statistical Analysis Plan

Protocol Title:	A Phase 1, Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of AMG 510 in Subjects of Chinese Descent With Advanced/Metastatic Solid Tumors With *KRAS p.G12C* Mutation (CodeBreak 105)
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Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	10DEC2019	
Amendment 1 (v2.0)	25AUG2021	To address protocol amendment 3.0, updated section 3.1, 3.2, 7.1 and 7.2 by including cohort 2 enrolment if more than 1 DLT observed in first 6 subjects. Section 5: added definition for relative dose intensity; updated definition for BOR, PFS and PFS censoring rule table. Section 9.4: added height, baseline TNM staging, smoking history; removed stages, prior immunotherapy treatment. Section 9.5.2: updated wording to be clear; added to allow for summary of efficacy endpoints assessed by local investigator. Section 9.6.3: added summary and listing for Hy's law cases.
Amendment 2 (v3.0)	31JAN2022	Section 4.2: added subgroup analysis by cancer type Section 6.3.2: added Efficacy Sensitivity Analysis Set Section 9.5: • updated Table 9-1 has by adding sensitivity analysis • updated to specify all primary efficacy analyses are based on local investigator assessment, and sensitivity efficacy analyses are based on central review assessment
Amendment 3 (v4.0)	17FEB2022	Section 5: • updated TEAE and TRAE definitions

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List of Abbreviations and Definition of Terms

Abbreviation	Explanation
AE	adverse event
AUC	area under the plasma concentration time curve
BOR	best overall response
C_{max}	maximum observed plasma concentration
CR	complete response
CI	confidence interval
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DLT	dose-limiting toxicity
DLRT	dose level review team
DOR	duration of response
DoSD	duration of stable disease
DRT	data review team
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
GSO	Global Study Operation
IPD	important protocol deviation
KM	Kaplan Meier
KRAS	Kirsten rat sarcoma
LTFU	long term follow-up
MedDRA	medical dictionary for regulatory activities
MRI	magnetic resonance imaging
NE	not evaluable
OR	objective response
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetics
PO	administered orally
PR	partial response
QD	once daily

Abbreviation	Explanation
QTc	corrected QT interval
QTcF	**Fridericia-corrected QT interval**
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SFU	safety follow-up
TEAE	Treatment emergent adverse event
t_{max}	time to achieve C_{max}
TTR	time to response
WHO	World Health Organization

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol amendment 4 for study 20190147 AMG 510 dated 05 January 2022. The scope of this plan includes the interim analysis, the primary analysis and final analyses that are planned and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of AMG 510 in adult subjects of Chinese descent with *KRAS p.G12C*-mutant advanced/metastatic solid tumors	• Subject incidence of dose-limiting toxicity (DLT), treatment-emergent adverse events, treatment-related adverse events, and changes in vital signs, electrocardiograms (ECGs), and clinical laboratory tests
• To characterize the pharmacokinetics (PK) of AMG 510 in subjects of Chinese descent when administered orally (PO)	• PK parameters of AMG 510 including, but not limited to, maximum observed plasma concentration (C_{max}), time to achieve C_{max} (t_{max}), and area under the plasma concentration time curve (AUC)
Secondary	
• To evaluate the preliminary efficacy of AMG 510 as a mono-therapy in subsets of solid tumors with the *KRAS p.G12C* mutation	• Objective response, duration of response, progression-free survival (PFS), disease control, time to response (TTR), and duration of stable disease measured by computed tomography (CT) or magnetic resonance imaging (MRI) and assessed per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 guidelines

2.2 Hypotheses and/or Estimations

No statistical hypothesis will be tested.

3. Study Overview

3.1 Study Design

This is a non-randomized, open-label, multi-center phase 1 study to evaluate safety, tolerability, PK, and preliminary efficacy of AMG 510 PO QD in subjects of Chinese descent with KRAS p.G12C-mutant advance/metastatic solid tumors. This study will be conducted at sites in Hong Kong and Taiwan.

Up to 18 subjects will be enrolled into the study. Enrollment into the first dose level cohort (cohort 1) may be from any eligible *KRAS p.G12C*-mutant advanced/metastatic solid tumor type. Six initial subjects will be enrolled into cohort 1 and will receive 960 mg of AMG PO QD. If ≤1 dose-limiting toxicity (DLT) is observed in the first 6 subjects, up to 6 additional subjects may be enrolled into cohort 1 to collect additional PK, safety, and preliminary efficacy at the 960 mg dose. If ≥ 2 DLT are observed in the first 6 subjects in cohort 1, an additional 6 subjects will be enrolled into a second dose level cohort (cohort 2), wherein the dose will be reduced to 720 mg AMG 510 PO QD. If ≤1 DLT is observed in the first 6 subjects in cohort 2, up to 6 additional subjects may be enrolled in cohort 2 to gather additional PK, safety and preliminary efficacy at the 720 mg dose.

The safety and tolerability data from the first 6 subjects at the 960 mg dose level will be reviewed by a Dose Level Review Team (DLRT) 21 days after receiving the first dose AMG 510. The DLRT will recommend whether cohort 1 should be continued at 960 mg or be modified and whether an additional 6 subjects could be enrolled in cohort 1 or if the 720 mg dose cohort (cohort 2) should be opened. If the DLRT makes the recommendation to enroll the next 6 subjects at the 720 mg AMG 510 dose in cohort 2, the DLRT will again review safety and tolerability data when the sixth enrolled subject at the 720 mg dose has the opportunity to receive AMG 510 for 21 days. The DLRT will recommend whether cohort 2 should be continued at 720 mg or be modified and whether an additional 6 subjects could be enrolled in cohort 2. The dose modification strategy is described in Protocol Section 6.2. Administration of AMG 510 may continue until there is evidence of disease progression, intolerance to study medication, or withdrawal of consent.

Subjects will have a safety follow-up (SFU) visit approximately 30 (+7) days after the last dose of AMG 510 or before any new anticancer treatment is started, whichever occurs first. The SFU visit will be the end of visit for each subject.

3.2 Sample Size

Up to 18 subjects will be enrolled in this study. Six DLT-evaluable subjects will be enrolled in cohort 1. If the 960 mg dose (cohort 1) is recommended to be safe and tolerable by the DLRT, up to 6 additional subjects may be enrolled in cohort 1 to gather additional safety, PK, and preliminary efficacy data (up to 12 subjects total enrolled in the study) at the 960 mg dose. Alternatively, if the DLRT recommends to open cohort 2 (720 mg dose), 6 DLT-evaluable subjects will be enrolled in cohort 2. If the DLRT then make the recommendation to continue cohort 2 at 720 mg, up to 6 additional subjects (up to 18 subjects total enrolled in the study) may be enrolled in cohort 2 to gather additional PK, safety, and preliminary efficacy at the 720 mg dose.

The sample size of 6-DLT evaluable subjects in the dose exploration phase for DLRM is based on practical considerations and is consistent with conventional oncology studies. With 6 DLT evaluable subjects, there is a 47% to 91% probability of observing at least 1 DLT if the true DLT rate is 10% to 33%.

3.3 Adaptive Design

De-escalation to a lower dose will be decided in the Dose Level Review Team.

4. Covariates and Subgroups

4.1 Planned Covariates

There are no planned covariates for this study.

4.2 Subgroups

Subgroup analyses for selected secondary endpoints (ORR and PFS) may be performed by cancer type (NSCLC, Colon cancer and Pancreatic cancer).

5. Definitions

AUC:

The area under the plasma drug concentration-time curve (AUC) reflects the actual body exposure to drug after administration of a dose of the drug.

Baseline:

For any variable, unless otherwise specified the baseline is the last non-missing assessment taken prior to the first administration of AMG 510 treatment. Where baseline measurements are taken on the same day as AMG 510 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 in Triplicate:

The mean of the three triplicate ECG results should be calculated for baseline. If fewer than three triplicate ECG results are available, the mean of available triplicate 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):

The best overall response for a subject is the best observed disease response per RECIST v1.1.

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, consecutive scan at least 4 weeks after the first documentation of response. A BOR of SD requires an on-study imaging of SD or better no earlier than 5 weeks after cycle 1 day 1, otherwise the BOR will be not evaluable (NE). Please see the details in Protocol Appendix 8 and refer Appendix A for deriving BOR calculation algorithm.

Change from Baseline:

Change from Baseline is the arithmetic difference between post-dose assessment and Baseline value.

Change (absolute) from Baseline = (Post-baseline Value - Baseline Value)

Percent Change from Baseline = [(Post-baseline Value-Baseline Value) / Baseline Value] ×100

Diseases Control Rate (DCR):

Diseases Control Rate is defined as the proportion of subjects in whom the best overall response is determined as CR, PR, or SD.

DLT:

A DLT is defined as any adverse event meeting the criteria listed in Protocol Section 6.2.2 occurring during the first treatment cycle of AMG 510 (day 1 through day 21) where a relationship to AMG 510 cannot be ruled out.

Duration of Response (DOR):

The duration of response is defined as time from first evidence of confirmed PR or CR to disease progression or death due to any cause, whichever occurs first. DOR will be calculated only for subjects who achieve a confirmed BOR of PR or CR.

DOR (months)= (PD or death date – response start date +1) x 12 / 365.25

Subjects will be censored following the censoring strategy described in Table 5-1.

Duration of Stable Disease (DoSD):

Duration of stable disease will be measured from the start of treatment to disease progression or death, whichever occurs first. DoSD will be calculated in subjects with best overall response SD. Subjects will be censored following the censoring strategy described in Table 5-1.

End of IP Administration (End of IP Admin):

End of IP Admin for each subject is defined as the date the decision was made to end IP as recorded on the End of Investigational Product Administration CRF page.

End of Study (Individual Subject):

End of study for each subject is defined as the date the subject last completed a protocol-specified procedure. The date will be recorded on the End of Study CRF page.

End of Study (End of Trial):

The end of study date is defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, safety follow-up), as applicable.

Investigational Product:

The term ‘investigational product’ is used in reference to AMG 510.

Last Investigational Product Dose Date:

The last IP date for each subject is defined as the latest date IP administered.

Objective Response Rate (ORR):

Objective response rate is defined as the proportion of subjects with a BOR of confirmed CR or PR.

Progression Fee-Survival (PFS):

The PFS is defined as interval from the first dose of AMG 510 until disease progression or death due to any cause, whichever comes first in the absence of subsequent anticancer therapy. The censoring rules for the progression-free survival analysis are detailed in Table 5-1.

PFS (months) = (PD or death date – start of treatment date +1) x12/365.25

Table 5-1. Date of Progression or Censoring for PFS

Situation (before data cutoff/ end of study)	Main Analysis	
	Date of Event or Censor	**Outcome**
Documented PD or death, no prior new anticancer therapy	Earlier of PD or death date	Event
No evaluable post-baseline tumor assessments, no death	Date of first dose	Censor
No documented PD, no death, but new anti-cancer therapy recorded.	Date of last evaluable assessment before start of new anti-cancer therapy	Censor
New anti-cancer therapy started before documented of PD or death	Date of last evaluable assessment before start of new anti-cancer therapy	Censor
No documented PD or death, no new anti-cancer therapy	Date of last evaluable assessment	Censor
Death or PD immediately after more than 1 consecutively missed tumor assessment	Date of last evaluable assessment prior to missing assessments	Censor

Relative Dose Intensity:

Relative dose intensity is calculated as actual dose intensity/planned dose intensity where

- Cumulative actual dose (mg) is defined as the total dose given during the study treatment exposure. For subjects who did not take any drug the cumulative actual dose by definition is 0 mg
- Actual dose intensity for subjects with non-zero duration of exposure is defined as: cumulative actual dose (mg)/duration of exposure (days), where duration of exposure = date of last non-missing dose – date of first dose +1. For subjects who did not take any drug the actual dose intensity is 0 mg/day.
- Cumulative planned dose is the per-protocol planned dose accumulated over the planned duration on the study treatment.

- Planned dose intensity for subjects with non-zero duration of exposure is defined as: cumulative planned dose (mg)/planned duration of exposure (days), where planned duration of exposure = date of last dose – date of first dose +1.

Safety Follow-Up:

The safety follow-up visit should occur approximately 30 (+7) days after last dose of AMG 510 or before any new anticancer treatment is started, whichever occurs first.

Study Day 1:

It is defined as the first day of the treatment being administrated to the subject.

Study Day:

Post-study day: study day = (date - date of Study Day 1) +1

Pre-study day: study day = (date - date of Study Day 1)

Time to Response (TTR):

Time to response is defined as time from the start of treatment until the first evidence of PR or CR. TTR will be calculated only for subjects who achieve a best overall response of confirmed PR or CR.

Treatment-Emergent Adverse Event (TEAE):

Events categorized as Adverse Events (AEs) 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 CRF and up to the End of Study date.

Treatment-Related Adverse Event (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 analysis of all endpoints, unless noted otherwise, will be conducted on the Safety Analysis Set.

6.1 Safety Analysis Set

The Safety Analysis Set is defined as all subjects that are enrolled and receive at least 1 dose of AMG 510.

6.2 Pharmacokinetic Analyses Set(s)

The PK Analysis Set will contain all subjects who have received at least dose of AMG 510 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.

6.3 Study-specific Analysis Sets

6.3.1 DLT Evaluable Sets

DLT Analysis Set is defined as DLT-evaluable subjects in the Safety Analysis Set. The analysis of DLT will be conducted on the DLT Analysis Set.

The DLT analysis set consists of subjects if either the subject experiences a DLT, or the subject does not experience a DLT and subject received at least 80% of the planned doses of investigational product within the 21-day DLT window.

6.3.2 Efficacy Sensitivity Analysis Sets

Efficacy Sensitivity Analysis Set will consist of subjects in Safety Analysis Set who have one or more measurable lesions at baseline as assessed by central review according to RECIST 1.1 criteria. This analysis set will be used for sensitivity analysis of efficacy endpoints based on central review assessment.

7. Planned Analyses

The following DLRT, primary, and final analyses of the study are planned.

7.1 Interim Analysis and Early Stopping Guidelines

7.1.1 Cohort 1 (Dose Exploration – first 6 DLT- evaluable subjects in cohort)

Safety data will be reviewed on an ongoing basis. The first DLRM will occur after the first 6 DLT-evaluable subjects enrolled in cohort 1 have the opportunity to receive 21 days treatment. In dose- level review meetings, Amgen, in consultation with the site investigators, will review all available cumulative data by cohort prior to making dose determination recommendations. Adverse events and DLTs observed in all subjects will be evaluated continuously and fully integrated into all dose level review meetings and considered in all enrollment and dosing recommendation. Additional details are provided in Protocol Appendix 3.

The DLRT will be composed of the investigations, Amgen Medical Monitor, Amgen Global Safety Officer (GSO), Amgen Early Clinical Development Manager, and Biostatistics representative. Additional members may be added as needed (eg, PK Scientist). A quorum, defined as the majority of actively screening and enrolling investigators or their qualified designee (ie, sub-investigator possessing hard copy documentation [eg, email] of the investigator's recommendation regarding the dose level review), must be in attendance for DLRM to proceed. The DLRM will be rescheduled if a quorum is not reached. Voting members of the DLRM will include the Amgen Medical Monitor, the Amgen GSO, and all actively screening and enrolling investigators or their qualified sub-investigator designee.

The Amgen Medical Monitor and GSO and the majority of actively screening and enrolling investigators participating in the DLRM must cast a positive vote indicating an acceptable safety profile was observed for AMG 510 to allow the dose level modification and/or cohort continuation/expansion to proceed. Available study data including demographics, smoking status (prior and current), medical history, concomitant medications, AEs, ECGs, vital signs, laboratory results, emerging PK or pharmacodynamics, and emerging efficacy data will be reviewed.

The following recommendations will be made by the DLRT:

- dose de-escalation recommendations
- number of subjects per cohort
- continuation, delay or termination of dosing
- change of the dosing schedule
- termination of the study

7.1.2 Cohort 2 (Dose Exploration – first 6 DLT-evaluable subjects in cohort)

If in cohort 1, DLRT makes the recommendation to open cohort 2 (720 mg), the second dose level review meeting will occur after the sixth subject enrolled in cohort 2 has had the opportunity to receive 21 days of treatment.

The same DLRT will be responsible for reviewing all cumulative available data by cohort. The same procedure and principal described in cohort 1 dose level review meeting will be applied in cohort 2 as well.

7.2 Primary Analysis

The primary analysis will occur after all subjects (6 to 12 subjects) enrolled in cohort 1 and after all 6 to 12 subjects enrolled in cohort 2 (if ≥ 2 DLTs are observed in the first 6 subjects in cohort 1) have had the opportunity to complete 6 months on study or have been withdrawn from study.

7.3 Final Analysis

A final analysis is planned after all cohorts have ended the study. Primary and final analyses may be combined in case all subjects have ended study close to the time point of the primary analysis.

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).

8.3 Handling of Missing and Incomplete Data

Descriptive statistics will be used to identify the extent of missing data. Missing or incomplete dates that are critical for the analysis (eg, date of death, adverse event start date) will be imputed. Details are described in Appendix B. Partial or missing death dates will be imputed prior to derivation of any endpoint that utilizes the date of death.

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 deviation. The clinical study team will identify and document the criteria for important protocol deviation.

8.5 Outliers

PK concentration data will be evaluated for outliners 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 Statistical Analysis System version 9.4 or later.

9. Statistical Methods of Analysis

9.1 General Considerations

Descriptive statistics will be provided for selected demographic, safety, PK and preliminary efficacy data by dose, and time as appropriate. Descriptive statistics on continues data will include means, medians, standard deviations and ranges, while categorical data will be summarized using frequency counts and percentages.

For time-to-event variables, the Kaplan-Meier (K-M) estimates and corresponding two-sided 95% confidence intervals for the median and quartiles will be provided. Graphical summaries of the data may also be presented. The K-M plot may also be provided. Subject listings for time-to-event endpoints may be provided instead of K-M estimates or Clopper Pearson exact confidence interval if the analysis set has fewer than 10 subjects.

9.2 Subject Accountability

The number and percent of subjects who were enrolled, 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, and last subject's end of study will 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. In addition, a separate listing of all inclusion and exclusion deviations will be provided.

9.4 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized using descriptive statistics:

- sex: (male vs. female)
- age group: (≤ 65,66-74, ≥ 75)
- age in years
- race
- height (centimeters)
- weight (kilograms)
- ECOG Performance Status (0,1,2)
- time from initial diagnosis to first dose of IP (months)
- histopathology (squamous, non-squamous)
- TNM stages (stage 0, I, II, III, IV)
- type of prior anticancer therapy
- prior lines of anti-therapy (1, 2, 3, >3)
- best response on last prior therapy
- prior radiotherapy for current malignancy (yes, no)
- prior surgery for current malignancy (yes, no)
- presence of brain metastases (yes, no)
- presence of liver metastases (yes, no)
- co-mutation of interest (if available from local testing)
- smoking history (never, former, current)

9.5 Efficacy Analyses

Table 9-1. Efficacy Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method (Specify Analysis Set if Safety Analysis Set is Not Used)	Sensitivity Analysis (Efficacy Sensitivity Analysis Set)
Objective Response (OR)	The proportion of subjects with an OR will be summarized along with a Clopper-Pearson exact confidence interval. Subjects without a post-baseline tumor assessment will be considered non-responders. Use local investigator review assessment per RECIST 1.1 criteria	Use central review assessment per RECIST 1.1 criteria

Endpoint	Primary Summary and Analysis Method (Specify Analysis Set if Safety Analysis Set is Not Used)	Sensitivity Analysis (Efficacy Sensitivity Analysis Set)
Disease Control	DCR will be summarized along with a Clopper-Pearson exact confidence interval. Subjects without a post-baseline tumor assessment will be considered non-responders. Use local investigator review assessment per RECIST 1.1 criteria	Use central review assessment per RECIST 1.1 criteria
DOR	DOR will be summarized with Kaplan-Meier quartiles and rates at selected time points (eg, > 3, > 6, > 9, > 12 months). Use local investigator review assessment per RECIST 1.1 criteria	Use central review assessment per RECIST 1.1 criteria
TTR	TTR will be summarized by the non-missing sample size (n), mean, standard deviation, median, minimum and maximum for responders. Use local investigator review assessment per RECIST 1.1 criteria	Use central review assessment per RECIST 1.1 criteria
PFS	PFS will be summarized with Kaplan-Meier quartiles and rates at selected time points (eg, > 3, > 6, > 9, > 12 months). Use local investigator review assessment per RECIST 1.1 criteria	Use central review assessment per RECIST 1.1 criteria
DoSD	DoSD will be summarized with Kaplan-Meier quartiles and rates at selected time points (eg, > 3, > 6, > 9, > 12 months). Use local investigator review assessment per RECIST 1.1 criteria	Use central review assessment per RECIST 1.1 criteria

Subject listings for time-to-event endpoints may be provided instead of K-M estimates or Clopper Pearson exact confidence interval if the analysis set has fewer than 10 subjects.

9.5.1 Analyses of Primary Efficacy Endpoint(s)

There is no primary efficacy endpoint.

9.5.2 Analyses of Secondary Efficacy Endpoint(s)

All efficacy endpoints are assessed by both local investigator review and central vendor review according to RECIST 1.1 criteria. All primary efficacy analyses are conducted with local investigator assessments based on Safety Analysis Set. The efficacy endpoints assessed by central review are summarized as sensitivity analysis, based on Efficacy Sensitivity Analysis Set.

Objective response rate (ORR)

The number and proportion of subjects with an objective response (OR), defined as CR+PR (assessed per RECIST version 1.1) will be summarized along with a

Clopper-Pearson exact 95% CI. Subject without a post-baseline tumor assessment will be considered as non-responders.

Duration of response (DOR)

DOR will be calculated only for subjects who achieve a best overall response of **confirmed** PR or CR Subjects will be censored following the censoring strategy described in the definition of PFS time in Table 5-1. The distribution of DOR, including the median and quartiles will be characterized using the Kaplan-Meier (K-M) method. The 95% CI for the median and quartiles of PFS will be constructed using the method of Klein and Moeschberger (1997) with log-long transformation.

Disease control rate (DCR)

Summary of disease control is measured by disease control rate (DCR),.

DCR will be summarized along with a Clopper-Pearson exact 95% confidence interval (Clopper and Pearson, 1934). Subjects without a post-baseline tumor assessment will be considered non-responders.

Duration of stable disease (DoSD)

DoSD will be calculated **only** in subjects with best overall response of SD. Subjects will be censored following the censoring strategy described in the definition of the PFS time and will be analyzed using the same method as described for DOR.

Time to response (TTR)

TTR will be summarized by the non-missing sample size (n), mean, standard deviation, median, minimum and maximum for responders, i.e., subjects who achieve best overall response of PR or CR.

Progression free survival (PFS)

The distribution of PFS, including median, with be estimated using the Kaplan-Meier method. PFS rate at the selected time points (at 3-month intervals) will be reported. The 95% CIs for the median and other quartiles of PFS will be constructed using the method Klein and Moeschberger (1997) with log-log transformation. The rates for selected durations (eg, > 3, > 6, > 9, > 12 months) will be reported and the 95% CI will be estimated using the methods by Kalbfleisch and Prentice (1980) with log-log transformation.

Listings of secondary efficacy endpoints will be produced for all subjects.

9.6 Safety Analyses

9.6.1 Analyses of Primary Safety Endpoint(s)

Table 9-2. Safety Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method
Primary	Unless otherwise specified, statistical analyses on safety endpoints will be done using subjects from the safety analysis set, which includes subjects that are enrolled and received at least 1 dose of AMG 510. The statistical methods are described in Section 9.6.2 through Section 9.6.6 and Section 9.7.1.

9.6.2 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 or later will be used to code all events categorized as adverse events to a system organ class and a preferred term.

Subject incidence of all treatment-emergent adverse events, fatal adverse events, serious adverse events, adverse events leading to withdrawal of investigational product, treatment-related adverse events and adverse events of interest will be tabulated by system organ class and preferred term.

Abnormal pregnancy outcome (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

The severity of each adverse event will be graded using The Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 criteria.

9.6.3 Laboratory Test Results

The analyses of clinical laboratory test will include summary statistics over time and/or changes from baseline over time will be provided for each scheduled post-baseline assessments. Tables of maximum shift from baseline to the worst on-study value will be provided for selected laboratory values with NCI-CTCAE grade. The parameters in Appendix C will be summarized.

Subject incidence of suspected 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 suspected of Hy's law case.

Unscheduled assessments will be included in the shift tables.

9.6.4 Vital Signs

The analysis of vital signs data will include summary statistics for each vital sign parameter for baseline and each scheduled post-baseline assessment and/or changes from baseline over time. Unscheduled assessments will be excluded.

9.6.5 Physical Measurements

Physical measurement data will be listed and reviewed for each subject. Summaries of changes from baseline over time may be provided. Unscheduled assessments will be excluded from table summary.

9.6.6 Electrocardiogram

Summaries over time and/or changes from baseline over time will be provided for all ECG parameters using central data. Subject's maximum change from baseline in QTcF will be categorized and the number and percentage of subjects in each group will be summarized. Subject's maximum post baseline values will also be categorized and the number of percentage of subjects will be summarized. Both scheduled and unscheduled assessments will be included in the determination of maximum change and value. All on-study ECG data will be listed.

9.6.7 Exposure to Investigational Product

Descriptive statistics of cumulative dose, number of cycles, duration of usage, number and percentage of subjects with dose modifications and reasons will be produced to describe the exposure to AMG 510. Subject-level data may be provided instead of the summary if the subject incidence is low or single dose is given.

9.6.8 Exposure to Concomitant Medication

The number and proportion of subjects receiving concomitant medication will be summarized by preferred term as coded by the World Health Organization Drug (WHO DRUG) dictionary.

9.7 Other Analyses

9.7.1 Analyses of Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Endpoints

For AMG 510, PK parameters including, but not limited to C_{max}, t_{max}, and AUC will be determined from the concentration-time profile using standard non-compartmental approaches and considering the profile over the complete sampling interval. 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.

10. Changes From Protocol-specified Analyses

There are no changes to the protocol specified analyses.

11. Literature Citations / References

Clopper C.J. and Pearson E.S. The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. Bimetrika Vol. 26., No. 4 (Dec., 1934): 404-413

Kalbfleisch, J.D. and Prentice, R.L. The Statistical Analysis of Failure Time Data, New York: John Wiley & Sons; 1980

Klein, J.P. and Moeschberger, M.L. Survival Analysis: Techniques for Censored and Truncated Data, New York: Springer-Verlag; 1997

World Health Organization 2018 Statistics. Accessed at: http://www.who.int/en/news-room/fact-sheets/detail/cancer on 01 August 2019.

12. Prioritization of Analyses

No priority of output is planned for this study.

13. Data Not Covered by This Plan

The analysis of Biomarkers and PRO endpoint is not covered in this plan.

14. Appendices

Appendix A. BOR Calculation Algorithm

BOR by investigator (used in interim analysis) will need to be derived based on Timepoint response collected on RECIST 1.1 CRF. Table 14-1 provides the BOR determination per RECIST 1.1 for trials where response confirmation is required. A BOR determined by Table 14-1 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. [redacted]

Table 14-1. 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.

*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.

Appendix B. Handling of Dates, Incomplete Dates and Missing Dates

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).

The reference date for the following rules is the date of first dose of AMG 510.

Imputation Rules for Partial or Missing Stop Dates

		Stop Date						
		Complete: yyyymmdd		Partial: yyyymm		Partial: yyyy		
Start Date		$< 1^{st}$ Dose	$\geq 1^{st}$ Dose	$< 1^{st}$ Dose yyyymm	$\geq 1^{st}$ Dose yyyymm	$< 1^{st}$ Dose yyyy	$\geq 1^{st}$ Dose yyyy	Missing
Partial: yyyymm	$= 1^{st}$ Dose yyyymm	2	1	N/A	1	N/A	1	1
	$\neq 1^{st}$ Dose yyyymm		2	2	2	2	2	2
Partial: yyyy	$= 1^{st}$ Dose yyyy	3	1	3	1	N/A	1	1
	$\neq 1^{st}$ 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 EOS/death date, impute as EOS/death date.

If a partial or complete stop date is present and the 'ongoing' or 'continuing' box is checked, then it will be assumed that the AE or con-med stopped and the stop date will be imputed, if partial.

Appendix C. Analyte Listing

Local Laboratory			
Chemistry	**Hematology**	**Coagulation**	**Lab parameter for shift tables**
Sodium Potassium Chloride Bicarbonate Total protein Albumin Calcium Magnesium Phosphorous Glucose BUN or urea Creatinine Total creatine kinase Total bilirubin Direct bilirubin ALP AST(SGOT) ALT(SGPT) Glomerular filtration rate (derived) TSH Total T3 (or free T3 per local standard) Free T4 Total cholesterol LDL HDL Triglycerides	RBC Hemoglobin Hematocrit MCV Platelets Calculated absolute neutrophil count (derived) WBC Differential • Total neutrophils • Eosinophils • Basophils • Lymphocytes • Monocytes **Urinalysis** Specific gravity pH Blood Protein Glucose Bilirubin Ketones Sodium (optional) Potassium (optional) Microscopic exam[a]: • Cellular casts • Granular casts • Hemoglobin casts • Hyaline casts • Mixed casts • WBC • RBC • Epithelial cells • Bacteria • Urine casts	PT or INR aPTT Fibrinogen (optional) D-Dimer (optional)	Albumin Alkaline Phosphatase Activated partial thromboplastin time Bilirubin Calcium Corrected Creatine Kinase Creatinine Fibrinogen Glucose Hemoglobin Potassium Lymphocytes Magnesium Sodium Neutrophils Platelets Protein Aspartate Aminotransferase Alanine Aminotransferase Leukocytes

ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = partial thromboplastin time; AST = aspartate aminotransferase; HepBsAg = hepatitis B surface antigen; HepCAb = hepatitis C antibody; HDL = high density lipoprotein; Hep = hepatitis; INR = international normalized ratio; LDL = low density lipoprotein; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell count; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; WBC = white blood cell count.

Note: For creatinine clearance calculation, Modification of Diet in Renal Disease formula should be used: GFR (mL/min/1.73 m2) = 175 x SCr (mg/dL)-1.154 x age-0.203 x 0.742 (if female) x 1.21 (if African American) x 0.763 (if Japanese) x 1.233 (if Chinese).

[a]Microscopic exam to be performed at the discretion of the investigator.