

Statistical Analysis Plan

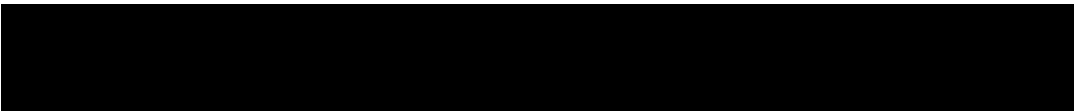
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Version Number	Date (DDMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	30Mar2020	
Amendment 1 (v1.1)	24May2022	• Added study schema which was missed previously. • Updated the DCR definition for RECIST 1.1 and iRECIST for providing more clarity. • Added OR definition which missed previously and also updated ORR, iBOR, DOR, PFS and DoSD definitions for more clear understanding on these definitions. • Updated the Vital Signs section for summarizing only planned visits.

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List of Abbreviations

Abbreviation	Explanation
AUC	Area under the plasma concentration time curve
C _{max}	Maximum observed plasma concentration
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
DES	Amgen data element standard
DILI	Drug induced liver injury
DLRM	Dose level review meeting
DLRT	Dose level review team
DLT	Dose limiting toxicity
ECG	Electrocardiogram
Echo	Echocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EDC	Electronic data capture
Electronic Source Data (eSource)	Source data captured initially into a permanent electronic record used for the reconstruction and evaluation of a trial.
Enrollment	When investigator decides that the subject has met all eligibility criteria
End of Follow-up	Defined as when the last subject completes the last protocol-specified assessment in the study
End of Study for Individual Subject	Defined as the last day that protocol-specified procedures are conducted for an individual subject
End of Study (primary completion)	Defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early
End of Study (end of trial)	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, long-term follow-up), as applicable
End of Treatment	Defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Conference on Harmonisation

IPIM	Investigational Product Instruction Manual
IRB	Institutional Review Board
MTD	Maximum tolerated dose
NCT	National Clinical Trials
PK	Pharmacokinetic(s)
RP2D	Recommended phase 2 dose
TBL	Total bilirubin
$t_{\max}$	Time to maximum observed plasma concentration
ULN	Upper limit of normal
OS	Overall survival
ORR	Objective response rate
PD	Progressive disease
QTc	Corrected QT (interval)
QTcF	Fridericia-corrected QT Interval
mg	Milli grams
DCR	Disease Control Rate
iCPD	Immune Confirmed Progressive Disease
iPR	Immune Partial Response
iSD	Immune Stable Disease
iPFS	Immune Progression Free-Survival
DoSD	Duration of Immune Stable Disease

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 for study 20180144, AMG 256 dated **20 March 2020**. The scope of this plan includes the primary analysis and the final analysis that are planned and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified.

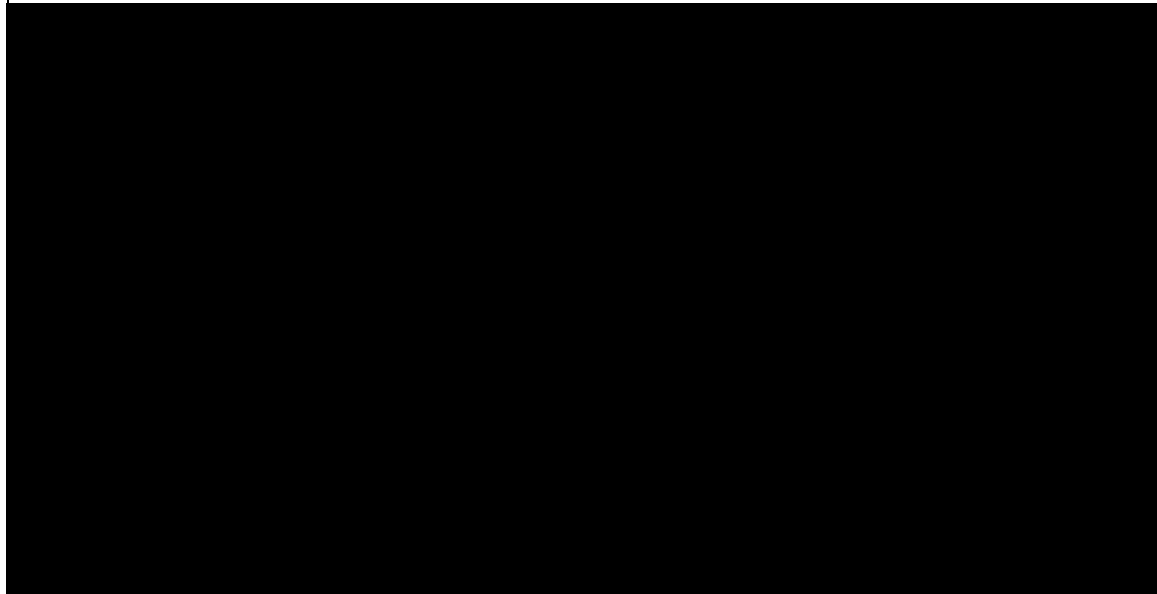
2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the safety and tolerability of AMG 256 in adult subjects with advanced solid tumors	Dose limiting toxicities (DLTs), treatment-emergent adverse events, treatment-related adverse events, and changes in vital signs, and clinical laboratory tests
To estimate the maximum tolerated dose (MTD) and/or biologically active dose (eg, recommended phase 2 dose [RP2D]) within investigated subject population groups	MTD and/or RP2D
Secondary	
To evaluate the pharmacokinetics (PK) of AMG 256	PK parameters of AMG 256 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)
To evaluate the preliminary antitumor activity of AMG 256	Objective Response (OR), per modified Response Evaluation

	Criteria in Solid Tumors (RECIST) 1.1 and iRECIST • Duration of Response (DOR) • Progression-free survival (PFS), 6-month and 1-year PS • Disease Control Rate (DCR) • Duration of stable disease • Overall Survival (OS), 1 and 2-year
• To assess the immunogenicity of AMG 256	• Subject incidence of anti-AMG 256 antibodies

Exploratory



2.2 Hypotheses and/or Estimations

This is a phase 1 study and no formal statistical hypotheses will be tested.

3. Study Overview

3.1 Study Design

This is a first-in-human (FIH), multicenter, non-randomized, open-label, phase 1 study to evaluate safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of AMG 256 in subjects with advanced solid tumors. AMG 256 will be administered by

intravenous (IV) infusion on [REDACTED] cycle or [REDACTED] of [REDACTED] cycle. The study may be conducted in Australia, Belgium, United Kingdom, United States, Poland, Japan and China. Other countries or regions may participate. The study will be conducted in 2 parts: Part 1 – Dose Escalation and Part 2 – Dose Expansion. Part 1 is intended to evaluate the safety, tolerability, PK and PD of AMG 256 and determine the maximum tolerated dose (MTD) in subjects with advanced solid tumors using a Bayesian Logistics Regression Model (BLRM) design. Part 2 will further evaluate the safety of the MTD and/or a biologically active dose (eg, recommended phase 2 dose [RP2D]) in specific tumor types. The dose expansion part of the study (Part 2) can be opened once the MTD/RP2D has been determined in Part 1. The dose escalation part of the study will consist of approximately 40 subjects and the dose expansion will consist of approximately 60 additional subjects. Dose escalation will be conducted in checkpoint inhibitor-naïve subjects; and dose expansion will be conducted in checkpoint inhibitor-exposed subjects with specific tumor types. The DLT evaluation period will be [REDACTED]. Based on emerging clinical efficacy data, the cancer types explored in the expansion part may be modified. Administration of AMG 256 (in part 1 and part 2) may continue until evidence of disease progression, intolerance to study medication, withdrawal of consent, or in the absence of the above up to 12 months if a subject achieves a complete response, and up to 24 months if partial response or stable disease is achieved.

Dose Escalation – Part 1

Dose escalation cohorts will estimate the safety, tolerability, PK, and PD of different doses of AMG 256 in subjects with advanced solid tumors who have not received treatment previously with a checkpoint inhibitor. Subjects will receive AMG 256 [REDACTED] or [REDACTED]. Dose escalation will begin with [REDACTED] dosing and [REDACTED] dosing will begin as indicated in the Study Schema ([Figure 1](#)). The [REDACTED] dosing may be initiated at lower doses or later than indicated, based on emerging safety, PK and/or preliminary response data. Dose escalation will begin with single subject cohorts treated at the lowest planned dose level of [REDACTED] mg [REDACTED]. The cohort size will be increased to N= 2-4 subjects after observation of treatment-related adverse events of grade 2 or higher; or escalation has reached the presumed efficacious dose; or is recommended by the dose level review team (DLRT) to further evaluate a cohort. To minimize the number of subjects treated at potentially toxic dose levels, subjects in each multiple subject cohort will be enrolled sequentially (**as per protocol section 11.10**).

- During dose escalation, [REDACTED] dosing subjects will be sequentially enrolled with a minimum of [REDACTED] between the first and second subjects being dosed within a cohort; and a minimum of [REDACTED] between the second, third and fourth subjects being dosed within a cohort.
- During dose escalation, [REDACTED] dosing subjects will be enrolled with a minimum of [REDACTED] between the first and second being dosed within a cohort; and a minimum of [REDACTED] between the second, third and fourth subjects within a cohort.

The sequential dosing of subjects within a cohort should be maintained as best possible for the [REDACTED] of treatment to minimize the potential for multiple subjects experiencing hypersensitivity reactions on the same day. The goal of the sequential dosing is to avoid multiple subjects receiving the same dose number on the same day during the first two cycles (ie, two subjects receiving cycle 1 [REDACTED] dose on the same day).

Dose escalation will follow the planned Study Schema schedule. If no DLT is observed, dose escalation will continue to the next planned dose cohort as per the Study Schema. Once a subject experiences a DLT, dosing for subsequent cohorts will be recommended using the dose level recommendation from the BLRM. The decision to advance to the next dose level will be recommended by the DLRT using the dose level recommendation from the BLRM, as appropriate, and by evaluating available safety data, laboratory, and PK information.

Intra-subject dose escalations are allowed on this study. Subjects who complete the DLT period may proceed to higher dose levels in the following treatment cycle once the next dose cohort has been deemed safe by the DLRT and after consultation with the sponsor if:

- The subject has not experienced any clinically significant $\geq$ grade 2 adverse events (deemed treatment related by the investigator) during treatment

Subjects who do not proceed to a higher dose may continue to receive additional cycles at the original dose. Dose escalation will continue until any of the following events:

- The highest planned dose level is determined to be safe and tolerable (minimum of 6 DLT-evaluable subjects)
- The MTD is identified
- BLRM recommends a dose level which already has 6 DLT-evaluable subjects

Additional subjects (up to 10) may be enrolled in one or more dose levels that have been shown to be safe and tolerable, defined as backfill enrollment. This backfill enrollment will be used to better estimate the RP2D and better characterize the safety, efficacy, pharmacokinetics and pharmacodynamics of AMG 256 and may be concurrent with dose escalation to identify the MTD.

Dose Expansion – Part 2

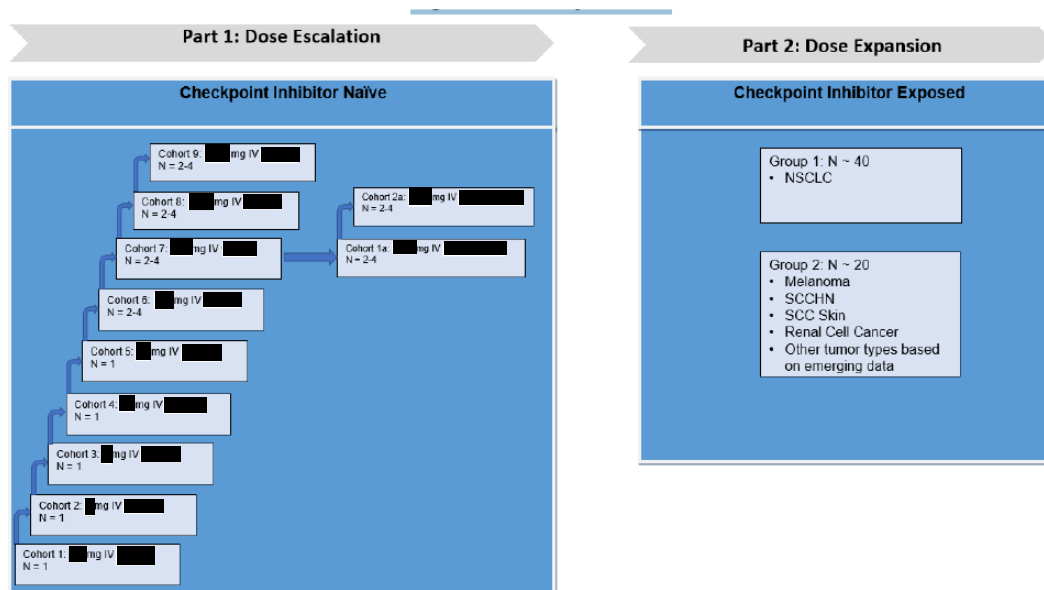
Upon completing the dose escalation part of the study and depending on data obtained, dose expansion may proceed. The RP2D/MTD will be administered in the dose expansion. Dose expansion will open to 2 groups with certain advanced solid tumors that are checkpoint-inhibitor exposed, as indicated below.

The first 6 subjects enrolled during expansion will be enrolled sequentially, with a minimum of 2 days between the subjects initiating treatment.

- Checkpoint Inhibitor Exposed
 - Group 1 (N= 40): Non-Small Cell Lung Cancer (NSCLC)
 - Group 2 (N= 20):
 - Melanoma
 - Squamous Cell Cancer of the Head and Neck
 - Squamous Cell Cancer of the Skin
 - Renal cell Cancer
 - Other tumor types based on emerging data

Dose expansion in all groups may be done concurrently.

Figure 1 Study Schema



3.2 Sample Size

It is anticipated that approximately 100 subjects will be enrolled in this study.

Approximately 30 subjects will be enrolled in the dose-escalation cohorts including up to 10 additional subjects as part of backfill enrollment. Up to 60 subjects will be enrolled in the dose-expansion cohorts.

3.3 Adaptive Design

Not Applicable

4. Covariates and Subgroups

4.1 Planned Covariates

The relationship of covariates to efficacy endpoints may be explored as appropriate.

4.2 Subgroups

Biomarker data may be incorporated in additional exploratory subgroup or multivariate analyses. The analyses of biomarkers may be performed after collection of all samples during the conduct of the study and therefore may be reported after the primary analysis of efficacy endpoints.

5. Definitions

Age at enrollment:

Subject age at enrollment will be determined using the age in years reported in the clinical database.

Enrollment:

A subject is considered enrolled on study day 1 when the investigator decides that the subject has met all eligibility criteria.

Enrollment Date:

Enrollment date is defined as the date when the investigator confirms that the subject has met all eligibility criteria and will be collected on the enrollment eCRF.

Investigational Product:

The term 'investigational product' is used in reference to AMG 256.

Baseline:

For any variable, unless otherwise specified the baseline is the last assessment taken prior to the first administration of AMG 256. 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 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 triplicates should be calculated. For all post-baseline ECGs, the mean of 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.

Fridericia-corrected QT Interval (QTcF):

The Fridericia correction will be calculated from the investigator reported QT (msec) and RR interval (msec), as follows: $QTcF = QT / (RR/1000)^{0.333}$.

Bazett-corrected QT Interval (QTcB):

The Bazett correction will be calculated from the investigator reported QT (msec) and RR interval (msec), as follows: $QTcB = QT / (RR/1000)^{1/2}$.

Change from Baseline:

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

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

Percent change from Baseline = [(Post-baseline Value – Baseline Value)/Baseline Value] x 100

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.

C_{max}:

The maximum concentration of drug obtained in the serum.

T_{max}:

The time takes to reach a maximum serum concentration of administered drug.

Body Mass Index (BMI):

Body Mass Index should be calculated using the following formula:

$BMI (kg/m^2) = weight (kg) / [height (cm)/100]^2$

Disease Control Rate (DCR) per RECIST 1.1 :

DCR is defined as the proportion of **subjects with objective response** or stable disease (SD) **>= 16 weeks (from the first dosing date) as per Modified RECIST 1.1.**

Disease Control Rate per iRECIST (iDCR):

iDCR is defined as the proportion **of subjects with immune objective response or immune-stable disease (iSD) $\geq$ 16 weeks (from the first dosing date) as per iRECIST.**

Dose Limiting Toxicity (DLT):

Investigators will determine whether an adverse event qualifies as a DLT per protocol **section 6.2.1.** The DLT window (ie, DLT-evaluable period) will be the first [REDACTED] of AMG 256 treatment (starting cycle 1, day 1).

Screening date:

Screening date is defined as the date the informed consent was signed.

Adverse Event (AE):

An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device or procedure.

Treatment emergent Adverse Event (TEAE):

A treatment-emergent adverse event is any adverse event starting on or after the first dose of investigational product (as determined by the flag indicating if the adverse event started prior to the first dose on the Events CRF) and up to including 30 days after the last dose of investigational product or the End of Study date, whichever is earlier.

Treatment-Related AE:

A treatment-related AE is any TEAE that per investigator review has a reasonable possibility of being caused by the investigational product and marked accordingly on the Adverse Events eCRF. **Event with missing/unknown relationship to treatment will be assumed to be treatment-related.**

Study Day 1:

Study day 1 is defined as the first day of administration of the investigational product after enrollment. The day prior to study day 1 is considered as day -1.

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)

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 when the subject completed the last protocol-specified procedure. The date will be recorded on the End of Study CRF page.

Last IP Dose Date:

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

End of Study (Primary Completion):

The **primary completion date** is defined as when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study was conducted as planned in the protocol or was terminated early.

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, long-term follow-up), as applicable.

Long Term Follow-Up:

Following the SFU visits, there will be a Long-term follow-up (LTFU) phone call at 6 months ($\pm$ 1 week) after the last dose to collect information on serious adverse events, concomitant medications to treat SAEs, start of new therapies, and disease status.

Safety Follow-up:

Upon permanent discontinuation from the study treatment for any reason, a safety follow-up visits will be performed approximately 30 (+7) days and 90 ($\pm$ 7) days after the last dose of AMG 256.

Objective Response (OR):

Confirmed objective response (defined as best overall response (BOR) of complete response (CR) or partial response (PR)) based on Modified Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1).

Immune Objective Response (iOR):

Confirmed immune objective response (defined as immune best overall response (iBOR) of immune complete response (iCR) or immune partial response (iPR)) based on immune Response Evaluation Criteria (iRECIST).

Objective Response Rate (ORR) per modified RECIST 1.1:

Objective response rate is defined as the proportion of patients with **confirmed** Best Overall Response (BOR) of CR or PR **based on modified RECIST v1.1.**

Immune Objective Response Rate (ORR) per iRECIST:

Objective response rate per iRECIST is defined as the proportion of patients with confirmed **immune** Best Overall Response (**iBOR**) of iCR or iPR **based on immune RECIST (iRECIST)**.

Best Overall Response (BOR) using modified RECIST 1.1:

Best overall response (BOR) for a subject is the best observed disease response per **Modified** RECIST v1.1. The best response will be recorded from the start of the study treatment until the end of treatment or disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). 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 best overall response of SD requires an on-study imaging of SD or better no earlier than 6 weeks after cycle 1 day 1; otherwise the best overall response will be not evaluable (NE). **Details of derivation of BOR are described in [Appendix E](#).**

Please refer Protocol Appendix 11.11 for more details.

immune-Best Overall Response (iBOR) using iRECIST criteria:

For iRECIST, the Best Overall Response (iBOR) is the best time point response recorded from the start of the study treatment until the end of treatment, taking into account any requirement for confirmation. For an iBOR of progression, the time point of iUPD that turned into iCPD is the time point of iBOR.

iBOR is defined as the best response in the following order: iCR, iPR, iSD, iCPD, or NE, where iCR, iPR and iCPD require confirmation by a repeat consecutive assessment at least 4 weeks after the first detection of radiographical response or progressive disease.

A best overall response of iSD requires an on-study imagine of iSD or better no earlier than 6 weeks after cycle 1 day 1; otherwise the BOR will be not evaluable (NE). Details for derivation of iBOR are described in [Appendix F](#).

Please refer Protocol Appendix 11.12 for more details.

Complete response (CR) per modified RECIST v1.1 criteria:

Disappearance of all target lesions, non-target lesions and normalization of tumor markers. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR) per modified RECIST v1.1 criteria:

Partial Response (PR) is defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Non target lesions must be non-Progressive Disease (non-PD).

immune Complete response (iCR):

Disappearance of all target lesions, non-target lesions and normalization of tumor markers. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

immune-Confirmed Progressive Disease (iCPD):

Per iRECIST, confirmation is required for progressive disease. Disease progression is confirmed only when two sequential assessments of disease progression (coded as iUPD or iCPD) with the second assessment at least 28 days after the first assessment of disease progression. When disease progression is confirmed the date of confirmed disease progression will be the date of the first assessment of disease progression.

Immune Confirmed Progressive Disease (iCPD) Requirements	
An overall response of iCPD can <u>only</u> be assessed immediately after a time point with overall response of iUPD ¹	
Cause of iUPD	iCPD Requirements
Target Lesion Progression	Additional worsening of target lesions as evidence by an increase of ≥ 5 mm in the target lesion SOM
Non-Target Lesion Progression	Any worsening in non-target lesions
New Target Lesions	Additional worsening of new target lesions as evidenced by an increase of ≥ 5 mm in the new target lesion SOM, or additional new target lesions
New Non-Target Lesions	Any worsening in non-target new lesion lesions or additional non-target new lesions
Any cause	New RECIST 1.1-assigned progression in another lesion category (ie, target or non-target lesions reach the definition of iUPD for the first time per Table 11-8 or Table 11-9 , or there are new lesions for the first time)

¹ Or immediately after an assessment of UE, NA, or ND if the assessment immediately before was iUPD

- Unable to evaluate (UE): Any lesion present at baseline which was not assessed or was unable to be evaluated leading to an inability to determine the status of that particular tumor for that time point
- Not Available (NA): Scan not available
- Not Done (ND): Radiographic imaging was not performed at this time point to evaluate the target lesions

immune Partial Response (iPR):

immune Partial Response (iPR) is defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Immune Stable Disease (iSD):

iSD is defined as when the requirements for iCR or iPR are not met, in the absence of iUPD.

Overall survival (OS):

Overall survival (OS) is defined as the time from the start of treatment (Study day 1) until event of death due to any cause.

OS time (Days) = Date of death – Study Day 1 + 1

OS time (Months) = (Date of death – Study Day 1 + 1)/30.4

Subjects still alive will be censored at the date last known to be alive. If the date last known to be alive is after the date that triggers the analysis (ie, the data cutoff date), the subject will be censored at the analysis trigger date.

Duration of Response (DOR) per modified RECIST 1.1:

The duration of response is defined as time from first **documentation** of PR or CR **until the first documentation of** disease progression or death due to any cause, **whichever occurs first. Subjects will be censored as per the censoring strategy described in the [Table 1](#) PFS definition.** DOR will only be derived for subjects with a confirmed PR or CR per **Modified RECIST 1.1.**

immune-Duration of response per iRECIST (iDOR):

The iDOR is defined as time from first **documentation** of iPR or iCR to date of confirmed disease progression (**i.e. iCPD**) or date of death due to any cause, **whichever occurs first.** iDOR will be calculated only for confirmed objective responders. **Subjects will be censored as per the censoring strategy described in the [Table 2](#) iPFS definition.**

Progression Free-Survival (PFS) using Modified RECIST:

The PFS is defined as interval from the start of treatment to **first documentation of** disease progression or death due to any cause (whichever comes first). The censoring rules for the progression-free survival analysis are detailed in [Table 1](#).

Table 1 Main PFS Definition

Situation	Date of Event or Censor	Outcome
No evaluable post-baseline tumor assessments, no death by data cutoff	Date of first dose	Censor
No surgical resection, no new anti-cancer therapy, did not withdraw consent to participate in the study and :		
Progression documented per Modified RECIST v1.1 before any death by data cutoff	Date of first observation date of disease progression	Event
No progression, but death recorded by data cutoff	Date of death	Event

No progression nor death by data cutoff	Date of last evaluable assessment	Censor
Surgical resection/new anti-cancer therapy started or withdraw consent to participate in the study and:		
Progression documented per Modified RECIST v1.1 before surgical resection/new anti-cancer therapy started or withdraw consent to participate in the study by data cutoff	Date of first observation date of disease progression	Event
Progression documented per Modified RECIST v1.1 after surgical resection/new anti-cancer therapy started or withdraw consent to participate in the study and alive by data cutoff	Date of last evaluable scan before start of new anti-cancer therapy/surgical resection	Censor
Subject died subsequently on or prior to data cutoff	Date of death	Event
No progression nor death by data cutoff	Date of last evaluable scan before start of new anti-cancer therapy/surgical resection	Censor

immune-Progression Free-Survival (iPFS) rate per iRECIST:

The iPFS is defined as interval from the start of treatment to date of confirmed disease progression (i.e. iCPD) per iRECIST or date of death due to any cause, (whichever comes first). **The censoring rules for the progression-free survival analysis are detailed in [Table 2](#).** See definition of Immune-Confirmed Progressive Disease for details on deriving date of confirmed disease progression.

Table 2. Main iPFS Definition

Situation (before data cutoff/ end of study)	Main Analysis	
	Date of Event or Censor	Outcome

Documented confirmed disease progression per iRECIST (prior to death or start of next anti-cancer therapy)	Date of first observation of disease progression, if and only if progression is confirmed	Event
No documented progression, but death recorded ^a	Date of death	Event
No evaluable post-baseline tumor assessments, no death	Date of first dose	Censor
No documented confirmed progression, no death, but start of new anti-cancer therapy recorded.	Date of last evaluable scan before start of new anti-cancer therapy	Censor
No documented confirmed progression, no death, no start of new anti-cancer therapy	Date of last evaluable assessment prior to data cutoff/end of study	Censor
Death or confirmed progression after 2 or more missed tumor assessment	Date of last scan with documented non-progression prior to missing assessments	Censor

^a Death will be counted as iPFS event even if after start of new anti-cancer therapy (instead of censor at last scan prior to start of new anti-cancer therapy).

Duration of stable disease per modified RECIST 1.1:

Duration of stable disease (DoSD) is defined from the start of the treatment to **first documentation of** disease progression per modified RECIST 1.1 or death **due to any cause, whichever occurs first**. DoSD will be calculated only in subjects with best overall response of SD. Subjects will be censored following the same censoring rules described in the definition of the PFS time in [Table 1](#).

Duration of Immune-stable disease (iDoSD) per iRECIST:

Duration of immune-stable disease (iDoSD) is defined from the start of the treatment to **confirmed** disease progression per iRECIST or death **due to any cause, whichever occurs first**. iDoSD will be calculated only in subjects with best overall response of iSD. Subjects will be censored following the same censoring rules described in the definition of the iPFS time in [Table 2](#).

6. Analysis Sets

The analysis of all endpoints, unless noted otherwise, will be conducted on the safety analysis set.

6.1 Full Analysis Set

Not Applicable

6.2 Safety Analysis Set

The Safety Analysis Set will consist of all subjects that are enrolled and receive at least 1 dose of AMG 256.

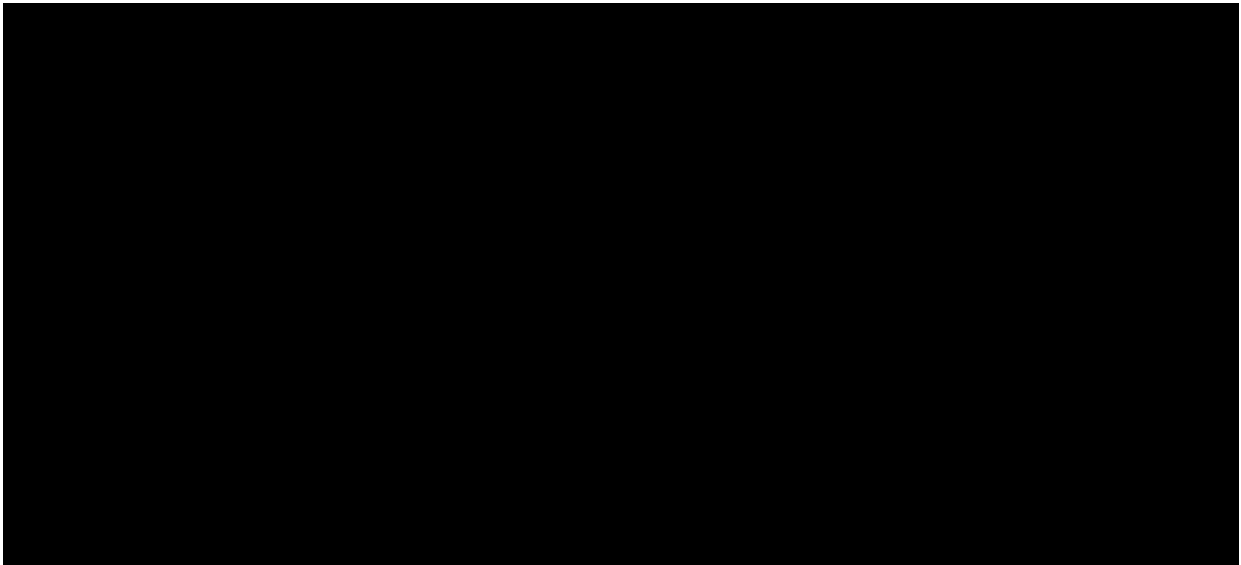
6.3 Per Protocol Set(s)

Not Applicable

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

Not Applicable

6.5 Pharmacokinetic/Pharmacodynamic Analyses Set(s)



6.6 Interim Analyses Set

Not Applicable

6.7 Study-specific Analysis Sets

6.7.1 DLT Evaluable Set

The analysis of DLT will be conducted on the DLT Analysis set defined as all subjects that are enrolled and receive at least 1 dose of AMG 256 with an evaluable DLT

endpoint. The DLT endpoint is evaluable if either: 1) the subject experiences a DLT, or 2) the subject does not experience a DLT within the DLT window.

6.7.2 RECIST Evaluable Analysis Set

The RECIST Evaluable Analysis set will contain all subjects that are enrolled to a dose expansion cohort and receive at least 1 dose of AMG 256 with at least one tumor lesion that is measurable in contrast-enhanced computed tomography (CT) as defined by **Modified** RECIST 1.1, with the following exceptions. The following subjects will be excluded from the RECIST Evaluable Analysis set: 1) subjects who are lost to follow up and have no on study radiological assessments and 2) subjects who have been on study less than 8 weeks and have no on study radiological assessments.

7. Planned Analyses

7.1 Interim Analysis and Early Stopping Guidelines

Safety data will be reviewed on an ongoing basis. Based on accumulating toxicity information, BLRM will be used to make dosing recommendations. In DLRMs, Amgen, in consultation with the site investigators, will review the BLRM recommended dose level and will review all available cumulative data by cohort prior to making dose escalation recommendations. As a sensitivity analysis, a 1-parameter Continual Reassessment Method model may be used to estimate the dose-toxicity relationship and in particular to estimate the dose level with a 25% DLT rate in order to help make dose escalation decisions. Adverse events and DLTs observed in all subjects will be evaluated continually and fully integrated into all DLRMs and considered in all enrollment and dosing decisions. If during the study there is any Grade 5 adverse event (or any two of the same Grade 4 adverse events) at least possibly related to AMG 256, further accrual will be suspended; Amgen will conduct a safety analysis and submit to the regulatory authority for review prior to resuming enrollment.

Key details of the BLRM model as used in this study are as follows. A bi-variate normal prior distribution (parameters “a” and “b”) is used for the BLRM model with bi-variate normal prior are as follows: the mean natural log (ln) of “a” $\ln(a)=-0.847$, standard deviation (SD) of “a” $SD(a)=1.275$, mean $\ln(b)=-0.611$ $SD(b)=3.269$ and correlation=0. The prior distribution is specified such that probability of dose-limiting toxicity (DLT) is 0.01 for the starting dose (1 mg) and 0.3 for the reference dose (100 mg), where the probability that the true DLT rate is ≤ 0.40 at the lowest planned dose is 0.90 and the probability the true DLT rate is ≤ 0.05 at the reference dose is 0.05. The BLRM

recommended next dose level is the level with the highest probability of the target toxicity probability interval (TPI), but with a less than 0.40 probability of an excessive or unacceptable TPI.

During dose expansion, if the observed rate of responses in a tumor type is less than 10% after n=10 and n=20 subjects then enrollment to the tumor type will be terminated due to futility. For purposes of assessing futility, a response is defined as an objective response per RECIST 1.1. The guidelines for early termination of enrollment for a tumor type due to futility are as follows:

Number of Treated Subjects in a Tumor Type	Enrollment Stopping Rule
10	0 responders
20	1 or fewer responders

If the true response rate is 5% then these termination guidelines result in a 78.7% probability of terminating tumor type enrollment at or prior to n=20 subjects. If the true response rate is 20% then there is an 86.4% probability of continuing enrollment past n=20 subjects.

During dose expansion, Amgen will conduct evaluations of the ongoing grade 4 or higher treatment-related adverse event rate to assess if the threshold for possible early trial termination has been reached. If this threshold is met, enrollment to dose expansion will be halted pending review of safety data by the DLRT. After receiving the DLRT recommendation, Amgen will choose to take one of the following actions.

- Terminate the trial
- Amend the protocol to potentially improve the benefit/risk for subjects (e.g. increase safety monitoring, modify dose/schedule, mandate premedication)
- Continue dose expansion without any changes

The stopping rules use a Bayesian approach proposed by Thall, Simon, and Estey (1995) to terminate the study if the posterior probability that the grade 4 or higher treatment-related adverse event rate is greater than 20% is > 80%. The stopping boundaries assume a prior distribution of Beta (0.40, 1.60) are presented in [Table 3](#) and the operating characteristics with pre-specified batch size of 10 new subjects per batch are presented in [Table 4](#). The operating characteristics in [Table 4](#) provide the probability of stopping the trial early for given hypothetical true rate of grade 4 or higher treatment-related adverse events, whereas the stopping criteria in [Table 3](#) are based on situations

where the empirical evidence would result in the posterior probability of $\geq 80\%$ that the true grade 4 or higher treatment-related adverse event rate is $\geq 20\%$.

Table 3 Stopping Boundary for Dose Expansion with Posterior Probability of 80% and Grade 4 or Higher Treatment-Related Adverse Event Limit of 20%

Number of subjects	Hold enrolment if observing this many grade 4 or higher treatment adverse events
10	≥ 4
20	≥ 6
30	≥ 9
40	≥ 11
50	≥ 13
60	Dose Expansion Complete

Table 4 Operating Characteristics with Batch Size of 10 Subjects

True grade 4 or higher treatment-related adverse event rate	Probability of early stopping of dose expansion	Average dose expansion sample size
0.10	2.1%	59.0
0.15	11.3%	55.4
0.20	33.1%	47.6
0.25	62.1%	37.0
0.30	84.8%	27.1

7.2 Primary Analysis

The primary analysis will occur when target enrollment is complete and each subject either completes 6 months on study or withdraws from the study. **Primary analysis will be based on locked database.**

7.3 Final Analysis

The final analysis will occur when target enrollment is complete for all study parts and all subjects have ended the study. Primary and final analysis may be combined in case all subjects have ended study close to the time point of the primary analysis. **Final analysis is based on final locked database to prevent future change.**

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 G](#).

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

Outliers may be identified via the use of descriptive statistics. All confirmed outlier data will be included in the analyses presented in this statistical analysis plan unless there is sufficient scientific justification to exclude them.

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

8.6 Distributional Characteristics

Where appropriate, the assumptions underlying the proposed statistical methodologies will be assessed. Data distribution will be explored, if required, data transformations or alternative non-parametric methods 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, pharmacodynamic and biomarker data. Unless otherwise specified, descriptive summaries will be presented by planned dose level and schedule. Descriptive statistics on continuous data will include mean, median, standard deviation and range, while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may also be presented.

Confidence intervals (CI) for proportions will be estimated using an exact method proposed by Clopper-Pearson (1934). Kaplan-Meier methods will be used to estimate the median and percentiles for time to event endpoints with CI calculated using the Brookmeyer and Crowley (1982) method. Kaplan-Meier methods will be used to estimate landmarks for time to event endpoints (e.g. 1-year progression-free survival) with the Greenwood formula (Kalbfleisch and Prentice, 1980) used to estimate the standard error used in CI calculation.

9.2 Subject Accountability

The number and percent of subjects who were enrolled, received investigational product, discontinued from investigational product (including reasons for discontinuation), completed study, discontinued the study (including reasons for discontinuation) will be summarized by treatment group. Key study dates for the first subject enrolled, last subject enrolled, and last subject's end of study will also 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 course of the study. Eligibility deviations are defined in the protocol. 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

Demographic characteristics including age, age groups (18 to 65, 66 and above), sex, race, ethnicity and baseline characteristics, which may include height, weight, Eastern Cooperative Oncology Group (ECOG) performance status, baseline disease stage, number of prior radio, chemo, antibody, Molecular targeted and Oncolytic therapies will be summarized for each cohort using descriptive statistics.

If multiple races have been reported for a subject, the subject will be categorized as multiple. A listing of the demographic and baseline characteristics will be provided. Lists of medical/surgical history, including prior chemotherapy, previous treatment radiotherapy, and prior cancer-related surgery will also be provided.

9.5 Efficacy Analyses

Table 5 Secondary Efficacy Endpoint Summary Table

Endpoint	Statistical Analysis	Analysis Set
Objective Response (OR), per modified RECIST 1.1	The proportion of subjects with an objective response per modified RECIST 1.1 along with corresponding exact 95% CI will be calculated using the Clopper-Pearson method (Clopper and Pearson, 1934) by tumor type and planned dose level. Waterfall plots for the maximum percent decrease from baseline in sums of longest diameters will also be provided. This analysis will be performed on RECIST evaluable and safety analysis set.	RECIST Evaluable Analysis Set, Safety Analysis Set
Immune Objective Response (iOR), per iRECIST	The proportion of subjects with an objective response per iRECIST along with corresponding exact 95% CI will be calculated using the Clopper-Pearson method (Clopper and Pearson, 1934) by tumor type and planned dose level. This analysis will be performed on RECIST evaluable and safety analysis set.	RECIST Evaluable Analysis Set, Safety Analysis Set
Disease Control Rate (DCR) per modified RECIST 1.1	The proportion of subjects with disease control per modified RECIST 1.1 along with corresponding exact 95% CI will be calculated using the Clopper-Pearson method (Clopper and Pearson, 1934) by tumor type and planned dose level.	RECIST Evaluable Analysis Set
Immune Disease Control Rate per iRECIST (iDCR)	The proportion of subjects with disease control per iRECIST along with corresponding exact 95% CI will be calculated using the Clopper-	RECIST Evaluable Analysis Set

Endpoint	Statistical Analysis	Analysis Set
	Pearson method (Clopper and Pearson, 1934) by tumor type and planned dose level.	
Duration of Response (DOR) per modified RECIST 1.1 Immune Duration of Response per iRECIST (iDOR)	- Descriptive statistics will be presented by tumor type and planned dose level. - Kaplan-Meier methods will be used to estimate the time of event curve. - DOR will be summarized using KM quartiles (Q1 [25th percentile], Median, Q3 [75th percentile]. These point estimates will be accompanied by 2-sided 95% confidence interval of KM quartiles. - KM estimates along with its 95% CI will be reported at 3, 6, 9 and 12 months using Kaplan Meier Method. DOR will be presented for modified RECIST 1.1 and iRECIST.	RECIST Evaluable Analysis Set
Progression-free survival (PFS) per modified RECIST 1.1 Immune Progression-free survival (iPFS) per iRECIST	- Descriptive statistics will be presented by tumor type and planned dose level. - Kaplan-Meier methods will be used to estimate the time of event curve. - PFS will be summarized using KM quartiles (Q1 [25th percentile], Median, Q3 [75th percentile]. These point estimates will be accompanied by 2-sided 95% confidence interval of KM quartiles. - KM estimates along with its 95% CI will be reported at 3, 6, 9 and 12 months using Kaplan Meier Method.	RECIST Evaluable Analysis Set

Endpoint	Statistical Analysis	Analysis Set
	PFS will be presented for modified RECIST 1.1 and iRECIST.	
Duration of Stable Disease (DoSD) per modified RECIST 1.1 Immune Duration of Stable Disease (iDoSD) per iRECIST	- Descriptive statistics will be presented by tumor type and planned dose level. - Kaplan-Meier methods will be used to estimate the time of event curve. - DoSD will be summarized using KM quartiles (Q1 [25th percentile], Median, Q3 [75th percentile]. These point estimates will be accompanied by 2-sided 95% confidence interval of KM quartiles. - KM estimates along with its 95% CI will be reported at 3, 6, 9 and 12 months using Kaplan Meier Method. DoSD will be presented for modified RECIST 1.1 and iRECIST.	RECIST Evaluable Analysis Set
Overall Survival (OS)	- Descriptive statistics will be presented by tumor type and planned dose level. - Kaplan-Meier methods will be used to estimate the time of event curve. - OS will be summarized using KM quartiles (Q1 [25th percentile], Median, Q3 [75th percentile]. These point estimates will be accompanied by 2-sided 95% confidence interval of KM quartiles. - KM estimates along with its 95% CI will be reported at 6 and 12 months using Kaplan Meier Method.	RECIST Evaluable Analysis Set, Safety Analysis Set

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

Not Applicable

9.5.2 Analyses of Secondary Efficacy Endpoint(s)

Not Applicable

9.5.3 Analyses of Exploratory Efficacy Endpoint(s)

Not Applicable

9.6 Safety Analyses

9.6.1 Analyses of Primary Safety Endpoint(s)

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 AMG 256. The analysis of DLTs will be conducted on the DLT Analysis Set. Subject incidence of DLT will be tabulated by planned dose level. A table of DLT will be provided. The probability of a subject having a DLT by dose level will be estimated using a two-parameter BLRM model.

9.6.2 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 22.1 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 will be tabulated by system organ class and preferred term in descending order of frequency for highest dose group. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product or other protocol-required therapies, and significant treatment emergent adverse events will also be provided. Additionally treatment-related treatment-emergent adverse event, treatment-related serious adverse event will be tabulated by system organ class and preferred term. Subject incidence of device-related events, if applicable, will be tabulated by system organ class and preferred term.

Subject listings of Serious AEs, Fatal AEs and Deaths will be provided.

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

9.6.3 Laboratory Test Results

Individual clinical chemistry, hematology, coagulation and urinalysis data will be listed. Depending on the size and scope of changes in laboratory data the analyses of safety laboratory endpoints will include summary statistics over time and/or changes from baseline over time may be provided for each dose level.

Shifts in grades of safety laboratory values from baseline for selected laboratory values may also be provided. Unscheduled assessments data will be used in the shift tables.

9.6.4 Vital Signs

The summary statistics over time and/or changes from baseline over time by dose level will be produced for systolic/diastolic blood pressure, heart rate, respiratory rate, pulse oximetry, and temperature. **Vital parameters will be summarized at each planned visit time points.**

Shifts in scores for ECOG performance status scores between the baseline and each assessed time point will be tabulated. ECOG performance status scores will be summarized at each **planned visit** time points.

9.6.5 Physical Measurements

Physical measurements will be reviewed for each subject.

9.6.6 Electrocardiogram

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

Subjects' maximum change from baseline in QTcF will be categorized and the number and percentage of subjects in each group will be summarized for each dose level. 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 in each group will be summarized. The categories are ≤ 450 msec, $> 450 - 480$ msec, $> 480 - 500$ msec, > 500 msec.

Unscheduled assessments will be included in the determination of the maximum change and value.

All on-study ECG data may be listed and select parameters of interest plotted.

9.6.7 Antibody Formation

The number and percentage of subjects who have developed anti- AMG 256 antibodies (binding and if positive, neutralizing) at any time, at baseline and during post-baseline visits will be summarized by treatment group.

9.6.8 Exposure to Investigational Product

Details of AMG 256 administration will be listed for every subject.

Descriptive statistics will be produced to describe the exposure to investigational product by treatment group.

9.6.9 Exposure to Non-investigational Product

Not Applicable

9.6.10 Exposure to Other Protocol-required Therapy

Number and proportion of subjects receiving therapies of interest will be summarized by preferred term for each treatment group as coded by the World Health Organization Drug dictionary.

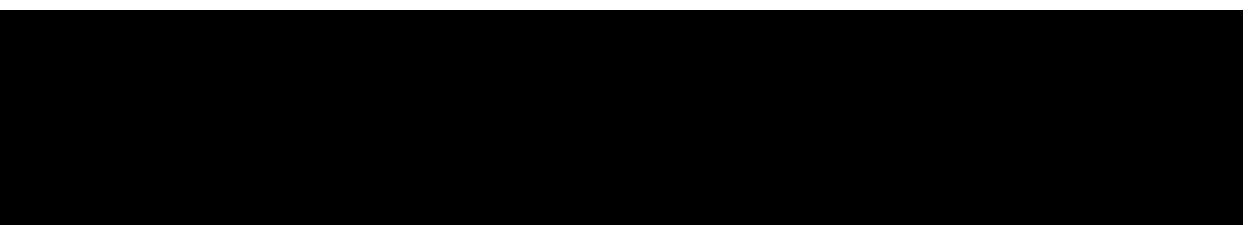
Descriptive statistics will be produced to describe the exposure to each of the protocol specified treatment by treatment group.

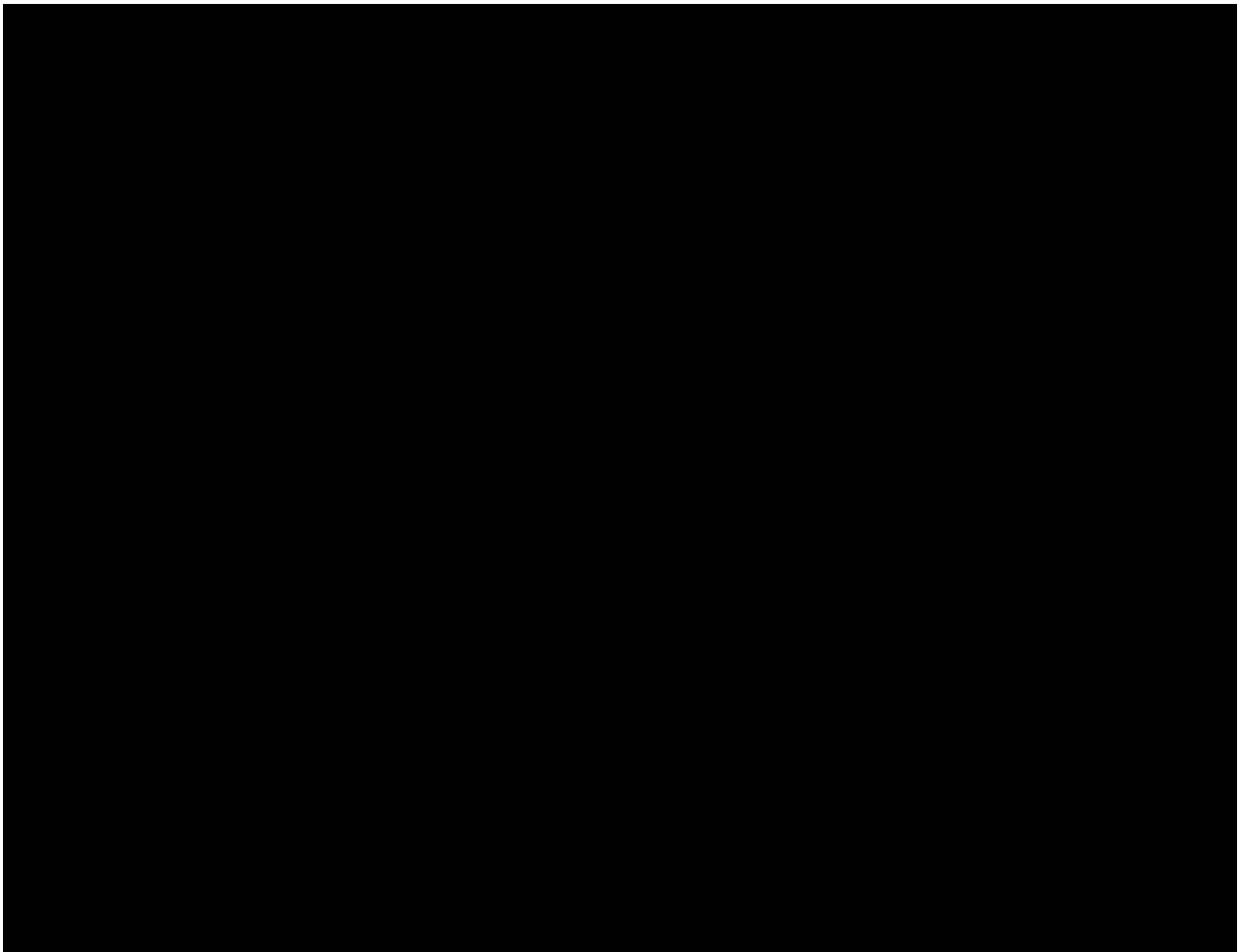
9.6.11 Exposure to Concomitant Medication

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. A subject listing of all prior and concomitant medications will be presented.

9.7 Other Analyses

Other analyses in the study include analyses for PK endpoints, and biomarker endpoints. **PK analyses will be provided by Amgen Clinical Pharmacology, Modeling & Simulation (CPMS). Details regarding the analyses will be provided in a separate analysis plan by CPMS. Biomarker analysis will be performed by biomarker team.**





9.7.2 Analyses of Clinical Outcome Assessments

Not Applicable

9.7.3 Analyses of Health Economic Endpoints

Not Applicable

9.7.4 Analyses of Biomarker Endpoints

Not Applicable

10. Changes From Protocol-specified Analyses

There are no changes to the protocol-specified analyses.

11. Literature Citations / References

AMG 256 Investigator's Brochure. Thousand Oaks, CA. Amgen Inc.
International Committee of Medical Journal Editors, Uniform Requirements for
Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical
Publication. 2013. <http://www.icmje.org/>

Brookmeyer, R. and Crowley, J. (1982) A Confidence Interval for the Median Survival Time, *Biometrics*, 38, 29 - 41.

Clopper CJ, Person ES. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika*. 1934; 26:404-413.

12. Prioritization of Analyses

Not Applicable

13. Data Not Covered by This Plan

Not Applicable

14. Appendices

Appendix A. Reference Values/Toxicity Grades

Not Applicable

Appendix B. Concomitant Medications

Not Applicable

Appendix C. Clinical Outcome Assessment Forms/Instruments

Not Applicable

Appendix D. Health Economic Forms/Instruments

Not Applicable

Appendix E. RECIST (v1.1) Criteria

Using time point assessment, the steps to derive BOR are in [Table 6](#). Confirmed BOR at time point X indicates the confirmed best overall response from all scans up to time point X. Interim BOR also consider last scan in case it is an unconfirmed response.

Table 6. Interim BOR Dérivation:

Situation	BOR
No evaluable post-baseline tumor assessment	Interim_BOR = NE (non-responders)
Subject has post-baseline scan(s) and still on study	- Derive confirmed_BOR: - At visit 1: Using the 1 scan and reference Table 7 to derive confirmed_BOR. - At each visit 2 onward: - Select current scan and prior scan (prior scan should be evaluable. If it is not evaluable go to an earlier scan, as possible, to a scan that is not 'NE'). - Use the 2 scans and reference Table 7 to derive BOR_temp. - Use rule CR>PR>SD>PD>NE, confirmed_BOR at this visit is the better between BOR_temp and confirmed_BOR at prior visit. - Derive Interim_BOR (could be confirmed or unconfirmed): - If latest scan is CR, interim_BOR = CR. - If latest scan is PR and confirmed_BOR is not CR, interim_BOR = PR. - Else, interim_BOR = confirmed_BOR.
Subject is off study (no potential further evaluation)	Just step 1 above. Assign Interim_BOR = confirmed_BOR

Example:

Post-baseline Visit	Timepoint scan (from eCRF)	Derive BOR_temp (per Table 7)	Derive confirmed_BOR (BOR_temp vs last confirmed_BOR)	Interim_BOR (confirmed_BOR vs current scan)
1	PR	SD	SD	PR
2	NE	SD	SD	SD
3	PR	PR	PR	PR
4	SD	SD	PR	PR
5	CR	SD	PR	CR

Table 7. BOR per RECIST 1.1 :

Criterion	Timepoint T1 Response	T1 ≥ 42 days after C1D1?	Timepoint T2 Response	T2 ≥ 42 days after C1D1?	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.

* Modification:

- Use C1D1 as start date, as baseline scan could be up to 21 days before C1D1.

Appendix F. iRECIST criteria

Confirmed iBOR is derived as follows:

Table 8. Confirmed iBOR Derivation:

Situation	iBOR
No evaluable post-baseline tumor assessment	confirmed_iBOR = NE (non-responders)
Subject has post-baseline scan(s) and still on study	1. Derive confirmed_iBOR: a. With only a single time point visit: Using the 1 scan and reference Table 8a to derive confirmed_iBOR. b. With only two time point visits: Using the 2 scans and reference Table 8b to derive confirmed_iBOR c. With three or more time point visits: - Separately for each time point visit: - o Derive the confirmed_iBOR for the respective time point visit (e.g. visit 1 or visit 2 or visit 6) using only 2 scans and reference Table 8b to derived confirmed_iBOR (the second scan must be the next subsequent scan with an evaluable result, if available) ▪ Example 1: get confirmed_iBOR for visit 1 using the visit 1 and visit 2 scans ▪ Example 2: get confirmed_iBOR for visit 2 using the visit 2 and visit 3 scans ▪ Example 3: get confirmed_iBOR for visit 6 using the visit 6 and visit 7 scans - Separately for each time point visit: - o Derive the confirmed_iBOR for the respective time point visit (e.g. visit 1 or visit 2 or visit 6) using 3 scans and reference Table 8c to derived confirmed_iBOR (the second and thirds scans must be the next two subsequent scan with an evaluable result, if available) ▪ Example 1: get confirmed_iBOR for visit 1 using the visit 1, visit 2 and visit 3 scans ▪ Example 2: get confirmed_iBOR for visit 2 using the visit 2, visit 3 and visit 4 scans ▪ Example 3: get confirmed_iBOR for visit 6 using the visit 6, visit 7 and visit 8 scans

	- When there are 3 or more scans for a time point visit (e.g. visit 1, visit 2 and visit 3 scan) then derive the overall confirmed_iBOR for the respective time point visit by taking the best confirmed_iBOR comparing the confirmed_iBOR using only 2 scans and the confirmed_iBOR using 3 scans where iCR>iPR>iSD>iPD>NE. - o Example: if time point visit 1 has a confirmed_iBOR of iSD using 2 scans but a confirmed_iBOR of iPR using 3 scans then the confirmed_iBOR for visit 1 is iPR. - Finally, derive the overall confirmed_iBOR by taking the best confirmed_iBOR over all time point visits using rule iCR>iPR>iSD>iPD>NE - o Example: if a study subject has a time point visit 1 confirmed_iBOR=iSD, time point visit 2 confirmed_iBOR=iPR and time point visit 6 confirmed_iBOR=iCR then the confirmed_iBOR=iCR for this subject.
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Table 8a. Confirmed iBOR at Time Point X* by iRECIST with 1 Time Point Response:

Time Point X Response	Time Point X ≥42 days after start of IP?	Confirmed iBOR* at Time Point X
iCR/iPR/iSD	Yes	iSD
iUPD/NE	Yes	NE
Any	No	NE

*This will be the confirmed iBOR for Time Point X when Time Point X is the only available disease assessment.

Table 8b. Confirmed iBOR at Time Point X* by iRECIST with 2 Time Point Response:

Time Point X Response (i.e. 1 st Time point Response)	1 st Time Point ≥42 days after start of IP?	2 nd Time point Response	2 nd Time Point ≥42 days after start of IP?	2 nd Time Point ≥ 28 days after 1 st Time Point?	Confirmed iBOR* at Time Point X
iCR	N/A	iCR	N/A	Yes	iCR
iPR	N/A	iPR/iCR	N/A	Yes	iPR
iCR/iPR/iSD	Yes	Any	N/A	No	iSD
iCR/iPR/iSD	No	iSD	Yes	N/A	iSD
iCR/iPR/iSD	Yes	iSD/iUPD	N/A	N/A	iSD
iCR/iPR/iSD	Yes	NE	N/A	N/A	iSD
iSD	Yes	Any	N/A	N/A	iSD
iUPD	N/A	iPR/iCR/iSD	Yes	N/A	iSD
iUPD/iCPD	N/A	iUPD/iCPD	N/A	Yes	iPD
iUPD/iCPD	N/A	iUPD/iCPD	N/A	NO	NE
iCR/iPR/iSD	No	iUPD	N/A	N/A	NE

iCR/iPR/iSD	No	NE	N/A	N/A	NE
iUPD/iCPD	N/A	iPR/iCR/iSD/NE	N/A	N/A	NE

*If there are exactly 2 time point responses (i.e. Time Point X response and a subsequent time point response), then the confirmed iBOR for Time Point X is described by [Table 8b](#). If there are 3 or more time point responses (e.g. Time Point X response and 2 or more subsequent time point responses) and the confirmed iBOR for Time Point X using rules in [Table 8c](#) is better than the confirmed iBOR for Time Point X using rules in [Table 8b](#) then the overall confirmed iBOR at Time Point X will be determined using the rules from [Table 8c](#). **N/A: Not Applicable.**

Table 8c. Confirmed iBOR at Time Point X by iRECIST with 3 Time Point Responses:

Time Point X Response (i.e. 1 st Time point Response)	1 st Time Point ≥42 days after start of IP?	2 nd Time point Response	2 nd Time Point ≥42 days after start of IP?	2 nd Time Point ≥ 28 days after 1 st Time Point?	3 rd Time point Response	3 rd Time Point ≥ 28 days after 1 st Time Point?	3 rd Time Point ≥ 28 days after 2 nd Time Point?	Confirmed iBOR* at Time Point X
iCR	N/A	iCR	N/A	Yes	Any	N/A	N/A	iCR
iCR	N/A	Any	N/A	N/A	iCR	Yes	N/A	iCR
iPR	N/A	iPR/iCR	N/A	Yes	Any	N/A	N/A	iPR
iPR	N/A	Any	N/A	N/A	iPR/iCR	Yes	N/A	iPR
iUPD/iCPD	N/A	iUPD/iCPD	N/A	Yes	Any	N/A	N/A	iPD
iCR/iPR/iSD	No	iUPD/iCPD	N/A	N/A	iUPD/iCPD	N/A	Yes	iPD
iCR/iPR/iSD	No	iUPD	N/A	N/A	iUPD/iCPD	N/A	Yes	iPD
iCR/iPR/iSD /iUPD/iCPD	No	NE	N/A	N/A	NE	N/A	N/A	NE
iUPD/iCPD	N/A	iPR/iCR/iSD/NE	No	N/A	iPR/iCR/iSD/NE	No	N/A	NE
iUPD/iCPD	N/A	iUPD/iCPD	N/A	No	iUPD/iCPD	No	No	NE
Any other scenarios not described above								iSD

*If there are 3 or more time point responses (e.g. Time Point X response and 2 or more subsequent time point responses) and the confirmed iBOR for Time Point X using rules in [Table 8b](#) is better than the confirmed iBOR for Time Point X using rules in [Table 8c](#) then the overall confirmed iBOR at Time Point X will be determined using the rules from [Table 8b](#).

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

Below imputation rules will be used to impute start date and stop date of AE and 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 study drug].

Start Date		Stop Date						Missing
		Complete: yyyyymmdd		Partial: yyyyymm		Partial: yyyy		
		< 1 st dose	≥ 1 st dose	< 1 st dose yyyyymm	≥ 1 st dose yyyyymm	< 1 st dose yyyy	≥ 1 st dose yyyy	
Partial: yyyyymm	= 1 st dose yyyyymm	2	1	n/a	1	n/a	1	1
	≠ 1 st dose yyyyymm		2	2	2	2	2	2
Partial: yyyy	= 1 st dose yyyy	3	1	3	1	n/a	1	1
	≠ 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 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 yyyyymm for the date last known to be alive equals yyyyymm 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 death date is in error, do not impute and censor the subject survival time.

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 death date is in error, do not impute and censor the subject survival time.

If a death date is totally missing:

Set death date to the day after the date last known to be alive. If the date last known to be alive is a partial date, set it to the first day of the month last known to be alive or first day of the year last known to be alive if month is also missing.