Statistical Analysis Plan

Protocol Title:	A Multicenter, Phase 1, Open-label, Dose-escalation and Expansion Study of AMG 340, a Bispecific Antibody Targeting PSMA in Subjects with Metastatic Castrate-resistant Prostate Carcinoma (mCRPC)
Short Protocol Title:	Open-label, Dose-escalation, and Expansion Study of AMG 340 in Subjects with Metastatic Castrate-resistant Prostate Carcinoma
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Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	17FEB2023	NA
Amendment 1 (v2.0)	31JUL2024	• Updates in definition of treatment emergent adverse event (Section 5.1.1).
		• Updates in definitions of RECIST 1.1 evaluable analysis set and PSA response evaluable analysis Set (Section 6.3).
		• Listings for ECOG is removed (Section 9.6.4), updates in exposure to IP (Section 9.6.8)

		• Updates in primary analysis text (Section 7.2)
		• Updates in changes from protocol specified analyses (Section 10)

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List of Abbreviations

Abbreviation	Explanation
AE	Adverse event
AUC	Area under the concentration-time curve
AUC_t	Area under the serum concentration-time curve from time zero to time of last measurable concentration
BOIN	Bayesian optimal interval
CI	Confidence interval
C_{max}	Maximum observed serum concentration
COVID-19	Coronavirus disease 2019
CR	Complete response
CRS	Cytokine release syndrome
CT	Computerized tomography
CTCAE	Common terminology criteria for adverse events
DLRM	Dose level review meeting
DLRT	Dose level review team
DLT	Dose limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern cooperative oncology group
eCRF	Electronic case report form
EOI	End of infusion
EOT	End of treatment
^{18}F-FDG	^{18}F-Fluorodeoxyglucose
FIH	First-in-human
[redacted]	
LPLV	**Last patient last visit**
mCRPC	Metastatic castrate-resistant prostate carcinoma
MedDRA	Medical dictionary for regulatory activities
MRI	Magnetic Resonance Imaging
^{99m}Tc MDP	^{99m}technetium methylene diphosphonate
MTD	Maximum tolerated dose
NA	Not applicable
PCWG3	Prostate cancer working group 3
PET	Positron emission tomography
PSA	Prostate-specific antigen
PSMA	Prostate-specific membrane antigen
Q3W	Once every 3 weeks
RECIST	Response evaluation criteria in solid tumors
RP2D	Recommended phase 2 dose
SSE	Symptomatic skeletal event
$t_{1/2}$ or $T_{1/2}$	Terminal half-life
TLS	Tumor lysis syndrome
T_{max}	Time to maximum observed serum concentration

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 5 for study 20210249 (formerly TNB585.001), AMG 340 (formerly TNB-585) dated 07 December 2022. The scope of this plan includes 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	
• Evaluate the safety and tolerability of AMG 340 when administered as monotherapy.	• Treatment-emergent adverse events • Treatment-related adverse events • Changes in vital signs and clinical laboratory tests
• Determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) for AMG 340 when administered as monotherapy.	• Dose-limiting toxicities (DLTs)

• Evaluate the pharmacokinetics (PK) of AMG 340 when administered as monotherapy.	• PK parameters of AMG 340 including, but not limited to:
	  • C_{max}
	  • Time to C_{max} (T_{max})
	  • Area under the concentration-time curve within a dosing interval (AUC_{0-t})

Secondary	
• Evaluate the clinical activity of AMG 340 when administered as monotherapy.	• Objective response (OR) per RECIST 1.1 • Overall survival (OS) • Progression-free survival (PFS) (radiographic and PSA) • 6-month landmark radiographic PFS • PSA response (30%, 50%, 70% and 90%) • Time to progression (radiographic and PSA)

	• Duration of response (DOR) per RECIST 1.1 • PSA DOR based on PSA50 • Time to symptomatic skeletal events (SSE)

Exploratory	
[redacted]	
• Evaluate immunogenicity of AMG 340	• Incidence of anti-AMG 340 antibody formation

2.2 Hypotheses and/or Estimations

In Part A, a safe and tolerable dose of AMG 340 will have evidence of anti-tumor activity in subjects with mCRPC as measured by objective response rate (ORR). In Part B, AMG 340 will improve ORR in subjects with mCRPC to 20% compared with the reference ORR of 5%.

3. Study Overview

3.1 Study Design

This is a phase 1 open-label, dose-escalation and expansion study evaluating the safety, PK, PD, and clinical activity of AMG 340 in subjects with progressive mCRPC who have received at least 2 or more prior lines of systemic therapy ('Line/regimen of therapy' is defined as a course of therapy [at least 1 cycle uninterrupted by progressive disease, cycle disruption due to toxicity or intolerance is acceptable]). To be eligible for enrollment in this study, subjects should have previously been exposed to, intolerant of, ineligible for, or declined therapy with both a novel anti-androgen (e.g., abiraterone, enzalutamide) and a taxane (e.g., docetaxel).

The study will consist of 2 parts:

- a monotherapy dose escalation (Part A) and
- a monotherapy dose expansion (Part B).

Part A: Monotherapy Dose Escalation:

Part A was initiated and employs a dose escalation design to evaluate the safety, tolerability, PK and PD profiles of single-agent AMG 340 administered Q3W. Up to 60 subjects with progressive mCRPC who have received at least 2 prior lines of therapy will be enrolled in Part A. Subjects should have previously been exposed to, intolerant of, ineligible for, or declined therapy with both a novel anti-androgen (e.g., abiraterone, enzalutamide) and a taxane (e.g., docetaxel). In Part A, cohorts have initially enrolled single subjects (Yuan et al, 2016). Proposed dose levels for AMG 340 are outlined in [redacted] but the number of dose levels tested will depend on safety, PK/PD, and activity data.

Upon the first occurrence of a grade ≥ 2 adverse event that is not unequivocally due to the subject's underlying malignancy or other extraneous cause, the corresponding cohort, and all subsequent cohorts in Part A, will be enrolled according to a BOIN design with the target toxicity rate of 30%. Cohorts will enroll a minimum of 3 subjects; up to 6 subjects may be enrolled concurrently (if transition from single subject cohorts to BOIN is triggered by a DLT, 6 subjects will be enrolled in that cohort). A maximum of 60 subjects will be enrolled in Part A. No more than 2 subjects should be dosed on the same day when enrolling new cohorts. Following the first assessment of BOIN dose escalation/de-escalation at a given dose level, additional subjects may be enrolled according to the BOIN criteria (Yuan et al, 2016).

If a response (partial response [PR] or complete response [CR]) is observed in a single subject cohort, cohorts enrolling thereafter will follow a BOIN design as above. The BOIN dose escalation and de-escalation boundaries (λ_e of 0.236 and a λ_d of 0.358) are shown in Table 3-1.

Table 3-1. Dose Escalation and De-escalation Boundaries

	Number of subjects treated at current dose cohort									
Actions	1	2	3	4	5	6	7	8	9	10
Escalate if # of DLTs ≤	0	0	0	0	1	1	1	1	2	2
De-escalate if # of DLTs ≥	1	1	2	2	2	3	3	3	4	4

DLT = dose limiting toxicity
Source: Yuan et al, 2016

Dose escalation has been started as planned with a Q3W dosing schedule, which may be altered after cumulative review of safety and PK data and a protocol amendment.

Administration of the first dose of AMG 340 to the first subject in each cohort must await completion of the first cycle (3 weeks) of the prior dose level, and a review of the safety data by the Dose Level Review Team (DLRT) (formerly referred to as the Safety Monitoring Group [SMG]). Input from biostatistical, PK and other experts will be sought as necessary. Cohorts *N*a (where N represents a Cohort number), b, c, etc. may be conducted in parallel. Not all dose level cohorts may be enrolled based on emerging safety data.

Based on the DLRT's ongoing review of emerging safety, PK/PD and clinical activity data, cohorts receiving intermediate doses between those proposed above may be implemented. Furthermore, it may become necessary to switch to an alternative dosing regimen. If the dosing schedule is switched, no dose modification should result in a

predicted steady state trough C_{max}, or AUC greater than that identified for the immediately prior lower dose level.

Part B: Monotherapy Dose Expansion:

Part B will evaluate the MTD (or RP2D) of AMG 340 monotherapy in up to 40 subjects with biopsy-proven progressive mCRPC. To be eligible for this study, subjects should have previously been exposed to, intolerant of, ineligible for, or declined therapy with both a novel anti-androgen (e.g., abiraterone, enzalutamide) and a taxane (e.g., docetaxel). Part B will be initiated once the MTD (or RP2D) has been selected based on data from the Part A. The MTD (or RP2D) and dosing frequency for Part B will be chosen by the DLRT based on safety, tolerability, PK/PD, and clinical activity data collected during the dose escalation portion of the study.

3.2 Sample Size

In Part A, at least 3 subjects are planned for enrollment into each cohort, with the goal of determining the MTD and/or RP2D of AMG 340. Approximately 60 subjects are anticipated in Part A; however, the total number of subjects in Part A will depend upon the occurrence of DLT events and how dose escalation progresses. If the unknown true toxicity rate/DLT rate is 33% in a given cohort, at least 2 DLTs are likely to be observed.

In Part B, up to 40 subjects will be enrolled to further evaluate safety and tolerability, to explore activity of AMG 340 and to evaluate the relationship between PD markers and PK, safety and clinical response. A sample size of 40 subjects was selected to achieve 92% power for testing the hypothesis on ORR at 1-sided alpha of 0.1 using the binomial exact test.

4. Covariates and Subgroups

4.1 Planned Covariates

Not applicable for this study.

4.2 Subgroups

[redacted]

5. Definitions

5.1 Study Endpoints

5.1.1 Primary Endpoints Definitions

Treatment-Emergent Adverse Event (TEAE):

Events categorized as Adverse Events (AEs) starting on or after the first dose of AMG 340 as determined by "Did event start before first dose of AMG 340" equal to "No" or missing on the **Adverse Events** eCRF and up to and including 90 days after the last dose of AMG 340 (however, if subject start a new line of therapy before 90 days follow-up visit, safety follow-up will be performed through 30 days post last dose of AMG 340 or until subject begins a new line of therapy, whichever occurs later) excluding events reported after End of Study Date. **Events that are directly related to metastatic castrate-resistant prostate carcinoma cancer or disease progression (including, but not limited to, preferred terms "prostate cancer", "progression of prostate cancer", "prostate cancer metastatic", "disease progression" etc.) will be excluded from TEAE analysis.**

Treatment-Related Adverse Event (TRAE):

A treatment-related AE is any treatment-emergent AE with the relationship flag on the **Adverse Events** eCRF indicating there is a reasonable possibility that the event may have been caused by AMG 340. 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.

Dose-limiting Toxicities (DLTs):

Investigators determine whether a TEAE qualifies as a DLT per the definition described in protocol section 6.2.1.4.1. For an adverse event to qualify as DLT, the start date must be within 21 days from the date of first dose of AMG 340.

5.1.2 Secondary Endpoints Definitions

Objective Response per RECIST 1.1 (OR):

OR is defined as a partial response (PR) or complete response (CR) per RECIST 1.1, confirmed by a repeat assessment at least 4 weeks later. Subjects who do not experience a confirmed PR/CR or do not have any follow-up tumor assessments will be regarded as non-responders. This endpoint applies only to subjects with measurable baseline disease per RECIST 1.1.

Details for derivation of Objective Response per RECIST 1.1 are described in Appendix B.

Overall Survival:

Overall survival is defined as the time from the date of Study Day 1 until death due to any cause:

OS time (Days) = date of death - Study Day 1 + 1.

Any subject not known to have died at the time of analysis will be censored based on the last recorded date on which the subject was alive.

PSA Progression:

PSA progression is defined as per PCWG3.

- After a decline in PSA from baseline to post-treatment, a PSA increase of ≥ 25% and ≥ 2 ng/mL above the nadir (the lowest value up to the assessed visit date). This PSA progression must be confirmed by a second consecutive value ≥ 3 weeks later.
- No decline in PSA from baseline, a PSA increase of ≥ 25% and ≥ 2 ng/mL from baseline at or beyond 12 weeks after treatment initiation.

Radiographic Progression:

A radiographic progression occurs if either of the following occurs:

- Progressive disease per RECIST 1.1 occurs.
- Bone disease progression as per PCWG3 occurs. Bone disease progression for the first post-treatment bone scan (e.g. Week 8) showing two or more additional lesions relative to screening/baseline must be confirmed by the next bone scan (e.g. Week 16) showing two or more additional lesions relative to first post-treatment bone scan (e.g. Week 8) at least 6 weeks later. Bone disease progression for scans after the first post-treatment scan (e.g. Week 16) showing two or more additional lesions relative to the first post-treatment bone scan (e.g. Week 8) can be confirmed by second scan showing persistence of the additional lesion relative to the first post-treatment scan (e.g. Week 8) at least 6 weeks later.

PSA Progression-free Survival (PSA PFS):

PSA PFS is defined as the interval from Study Day 1 to the earlier of a PSA progression or death from any cause; otherwise, PSA PFS is censored on the date of the last PSA measurement. If a subject has no baseline or post-baseline PSA measurement and a vital status of alive or unknown, PSA PFS will be censored at Study Day 1.

More details about censoring rules are included in Appendix D.

Radiographic Progression-free Survival (rPFS):

rPFS is defined as the interval from Study Day 1 to the earlier of a radiographic progression or death from any cause; otherwise, rPFS is censored based on the criteria in Appendix D.

PSA Response (PSA 30):

A PSA response (PSA30) is defined as a ≥ 30% decrease below baseline confirmed by a second consecutive value obtained 3 or more weeks later. An increase in PSA in the first 12 weeks does not preclude a response thereafter. Only subjects with measurable (i.e., > 0) baseline PSA will be evaluated for PSA response.

PSA Response (PSA 50):

A PSA response (PSA50) is defined as a ≥ 50% decrease below baseline confirmed by a second consecutive value obtained 3 or more weeks later. An increase in PSA in the first 12 weeks does not preclude a response thereafter. Only subjects with measurable (i.e., > 0) baseline PSA will be evaluated for PSA response.

PSA Response (PSA 70):

A PSA response (PSA70) is defined as a ≥ 70% decrease below baseline confirmed by a second consecutive value obtained 3 or more weeks later. An increase in PSA in the first 12 weeks does not preclude a response thereafter. Only subjects with measurable (i.e., > 0) baseline PSA will be evaluated for PSA response.

PSA Response (PSA 90):

A PSA response (PSA90) is defined as a ≥ 90% decrease below baseline confirmed by a second consecutive value obtained 3 or more weeks later. An increase in PSA in the first 12 weeks does not preclude a response thereafter. Only subjects with measurable (i.e., > 0) baseline PSA will be evaluated for PSA response.

Time to PSA Progression:

Time to PSA progression is defined as the interval from Study Day 1 to PSA progression; otherwise, time to PSA progression is censored based on the criteria in Appendix D.

Time to Radiographic Progression:

Time to radiographic progression is defined as the interval from Study Day 1 to radiographic progression; otherwise, time to radiographic progression is censored based on the criteria in Appendix D.

Duration of Response (DOR) per RECIST 1.1:

DOR is defined as the time from the date of an initial objective response per RECIST 1.1, which was subsequently confirmed, to the earlier of soft-tissue progression per RECIST 1.1 or death. Subjects who have not ended their response at the time of analysis will have DOR censored at their last evaluable tumor assessment by CT/MRI scan. This endpoint only applies to subjects with an objective response per RECIST 1.1.

Duration of PSA Response (PSA DOR):

PSA DOR is defined as the time from the date of initial PSA response (PSA 50), which was subsequently confirmed, to the earlier of PSA progression or death. Subjects who have not ended their response at the time of analysis will have PSA DOR censored on the date of their last PSA measurement. The endpoint only applies to subjects with a PSA response (PSA 50).

Details about the censoring rules are included in Appendix D.

Time to Symptomatic Skeletal Events:

Time to SSE is defined as time from Study Day 1 to the first SSE. Otherwise, SSE is censored at the last dose date of investigational product (AMG 340) or end of safety follow-up date, whichever is later.

A Symptomatic Skeletal Event (SSE) is defined as any of the following which is collected on the **Adverse Events** eCRF:

For Part A of the study, a list of preferred terms will be identified at the time of analysis for what constitutes an SSE.

For Part B: there is a separate event categories to identify them

- A symptomatic fracture which is any adverse event of fracture (ankle, hip, spinal, wrist or other) per CTCAE version 5.0.
- Radiation or surgery to bone.
- Spinal cord compression.

5.2 Study Time Points

Study Day 1:

Study Day 1 is defined as the date of the first dose of the AMG 340 administered to the subject.

End of Treatment:

End of treatment is defined as the date the decision was made to end of AMG 340 as recorded on the End of Treatment Status eCRF page.

End of Study for Individual Subject:

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

End of Study:

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 (i.e., Last subject last visit), following any additional parts in the study (e.g., long-term follow-up), as applicable.

Safety follow-up Visit:

Safety follow-up visit is defined as upon permanent discontinuation from the study treatment for any reason, a safety follow-up visit will be performed approximately 90 (+7) days after the end of the last dose of AMG 340 and/or product required therapies. However if subject starts a new line of therapy before 90 (+7) days follow-up visit, safety follow-up will be performed through 30 days post last dose of AMG 340 or until the subject begins a new line of therapy, whichever occurs later.

Long-term follow-up Visit:

Subjects will be followed for survival and/or the commencement of subsequent therapy via clinic visit, telephone, or chart review call every 6 months from the SFU visit for up to a maximum 3 years.

5.3 Demographics and Baseline Related Definitions

Age at enrollment:

Subject age at enrollment will be collected in years reported in the Demographics eCRF.

Baseline:

The baseline is defined as the last non-missing value on or prior to the pre-dose of AMG 340 assessments on cycle 1 day 1.

Change from Baseline:

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

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

Percent Change from Baseline:

Percent change from baseline is the arithmetic difference between post-baseline and baseline divided by baseline values times 100.

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

6. Analysis Sets

6.1 Safety Analysis Set

Safety analysis set defined as all subjects who have received at least 1 dose of AMG 340.

6.2 Pharmacokinetic/[redacted] Analyses Set

The Pharmacokinetic (PK) Analysis Set will include all subjects who have received at least 1 dose of AMG 340 and have at least 1 PK sample drawn post dose. These subjects will be evaluated for PK Analysis unless the number of data points required for analysis is not enough, or significant protocol deviations have affected the data, or if key dosing or sampling information is missing. The PK Analysis set will be used to conduct the analysis of PK data, unless otherwise specified.

6.3 Study-specific Analysis Sets

6.3.1 RECIST 1.1 Evaluable Analysis Set

RECIST 1.1 Evaluable Analysis Set is defined as all subjects who have received at least 1 dose of AMG 340, have measurable disease per RECIST 1.1 at baseline, and have the opportunity to be followed for at least 6 weeks from start of AMG 340 treatment. Subjects who stopped disease assessments prior to 6 weeks will be included in this analysis set if the **data snapshot date** is at least 6 weeks after their first study dose date.

This analysis set is used for the analysis of the radiographic-measured endpoints of objective response and duration of response (radiographic).

6.3.2 PSA Response Evaluable Analysis Set

PSA Response Evaluable Analysis Set is defined as all subjects who have received at least 1 dose of AMG 340, have a measurable (i.e., > 0) PSA at baseline, and have the opportunity to be followed for at least 9 weeks from start of AMG 340 treatment. Subjects who stopped disease assessments prior to 9 weeks will be included in this analysis set if the **data snapshot date** is at least 9 weeks after their first study dose date.

This analysis set is used for the analysis of PSA-measured endpoints that are PSA responses, PSA duration of response.

6.3.3 DLT Evaluable Analysis Set

DLT Evaluable Analysis Set defined as all subjects who are evaluable for DLTs. A subject is considered DLT evaluable if the subject has completed at least the first full treatment cycle or experienced a DLT during the first treatment cycle. This applies only for dose exploration part.

7. Planned Analyses

7.1 Interim Analysis and Early Stopping Guidelines

Amgen will conduct evaluations of the treatment and outcome of the CRS events treated with siltuximab on an ongoing basis to assess if the threshold for pausing siltuximab treatment has been reached as outlined in the table below. If these stopping rules are met, an adhoc DLRT will be triggered to review safety data and available PK, PD, and efficacy data. If recommended by DLRT, the use of siltuximab will resume. The stopping rules to trigger an adhoc DLRT to review siltuximab treatment use a Bayesian approach proposed by Thall, et al (1995); an adhoc DLRT will be triggered if the posterior probability that the CRS progression to grade 3 rate is greater than 30% is > 80% or the posterior probability that the CRS progression to grade 4 rate is greater than 10% is >80%; or observation of any grade 5 CRS after the event has been treated with siltuximab. The stopping boundaries presented below assume a prior distribution of Beta (0.6, 1.4) for progression to grade 3 CRS and a prior distribution of Beta (0.2, 1.8) for progression to grade 4 CRS. The evaluations could occur more frequently if necessary to address emerging safety concerns. If the triggered ad hoc DLRT coincide with regular DLRT, they may be combined.

Table 7-1. The Criteria for Evaluating the Use of Siltuximab

	Trigger DLRM if severity of any CRS event treated with siltuximab progresses to Grade 5	
Number of subjects treated with siltuximab	Or the number of subjects with severity of CRS progressed to Grade 3 after being treated with siltuximab is	Or the number of subjects with severity of CRS progressed to Grade 4 after being treated with siltuximab is
5	≥ 3	≥ 2
10	≥ 5	≥ 3
15	≥ 7	≥ 3
20	≥ 8	≥ 4
25	≥ 10	≥ 5
30	≥ 12	≥ 5
35	≥ 13	≥ 6
40	≥ 15	≥ 6

CRS = cytokine release syndrome; DLRM = dose level review meeting

7.2 Primary Analysis

The primary analysis will occur 6 months following the enrollment of the last subject in Arm B. The data will be analyzed once they have been entered, cleaned, and locked. **If we do not proceed with Arm B of the study, the primary analysis will be combined with the final analysis.**

7.3 Final Analysis

The final analysis will occur after all subjects have ended the study. The data will be analyzed once they have entered, cleaned, and locked.

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 receive and store all data to be used in the planned analyses. This study will use the RAVE database and pharmacokinetics, antibody, biomarkers, and central lab data outside of RAVE database. The database will be subjected to edit check outlined in the Data Management Plan (DMP). Additional details will be provided in the DMP and Data Acquisition Requirements Specification (DARS).

8.3 Handling of Missing and Incomplete Data

Subjects may miss specific data points for a variety of causes. In general, data could be missing due to a subject's early withdrawal from the study, a missed visit or inability to evaluate an endpoint at a particular point in time.

In general, the safety analysis set will be used without any imputation for missing data for the primary and secondary endpoints. Missing safety endpoints and antibody data will not be imputed, except for adverse events, concomitant medications, and death date as described in [redacted]

PK concentrations that are below the quantification limits will be set to zero when included in the non-compartmental model to compute PK parameters.

Missing or incomplete dates will be listed unless imputed as follows. An incomplete start date of an adverse event or concomitant medication taken will be handled by rules mentioned in [redacted]

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

8.5 Outliers

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

Descriptive statistics will be used to identify potential outliers in key variables. Suspected outliers will be included in the analyses unless there is sufficient scientific justification to exclude them.

8.6 Distributional Characteristics

Where appropriate, the assumptions underlying the proposed statistical methodologies will be assessed. 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 and validated in accordance with [redacted]. Standard macros will be used when available.

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 data by dose, dose schedule, and time as appropriate. Descriptive statistics on continuous data will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may also be presented.

9.2 Subject Accountability

The number and percent of subjects who were enrolled received AMG 340, completed AMG 340, discontinued from AMG 340 and reasons for discontinuing, completed study, discontinued study and reasons for discontinuing, will be summarized by cohort.

The number of subjects who signed informed consent but were not enrolled into the study will be tabulated by reason.

Key study dates for the first subject enrolled, last subject enrolled, last subject's end of AMG 340 and last subject's end of study will be presented.

The number and percent of subjects enrolled will be tabulated by study site.

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. The final IPD list is used to produce the summary of the IPDs table and list the subjects with IPDs. In addition, a separate listing of all inclusion and exclusion deviations will be provided. Important protocol deviations thought to potentially impact the safety of subjects or the interpretation of the analyses will be listed and tabulated using incidence and percentages by deviation type.

The number of subjects reporting Protocol Deviation due to COVID-19 will be summarized in a table. A protocol deviation listing of subjects impacted due to COVID-19 will also be provided.

9.4 Demographic and Baseline Characteristics

The following descriptive summaries of demographics and baseline characteristics will be summarized.

Demographics:

- Age (years) at enrollment (continuous summary statistics)
- Age categories (number and percentages of subjects < 65, ≥ 65, ≥ 75, and ≥ 85 years)
- Race (number and percentages of subjects in each category)
- Ethnicity (number and percentages of subjects in each category)

Baseline characteristics:

- Height and Weight (continuous summary statistics)
- ECOG performance status (frequency and percentages)

9.5 Efficacy Analyses

9.5.1 Analyses of Primary Efficacy Endpoints

Not applicable to this study.

9.5.2 Analyses of Secondary Efficacy Endpoints

Analyses of secondary efficacy endpoints are defined in Table 9-1. Listings may be provided instead if the number of subjects for analysis is small.

Table 9-1. Secondary Efficacy Endpoints Summary Table

Endpoint	Statistical Analysis	Analysis Set
Objective Response per RECIST 1.1	The proportion and subjects with an objective response per RECIST 1.1 along with the corresponding exact 95% CI will be calculated using the Clopper-Pearson method (Clopper and Pearson, 1934).	RECIST 1.1 Evaluable Analysis Set
	Waterfall plots for the maximum percent decrease from baseline in	RECIST 1.1 Evaluable analysis set and applicable for all subjects with baseline measurable

Endpoint	Statistical Analysis	Analysis Set
	sums of longest diameter will also be provided.	disease and with both a baseline at least one post-baseline evaluable tumor response assessment.
Overall Survival	The overall survival will be estimated using the Kaplan-Meier curve and 95% CI using Greenwood's formula to estimate the standard error of the landmark estimates, see Kalbfleisch, J.D. and Prentice, R. L. (Kalbfleisch and Prentice, 1980).	Safety Analysis Set
Progression Free Survival PSA	The median and other percentiles as appropriate, will be presented using the Kaplan-Meier curve and 95% CI using the Brookmeyer and Crowley (Brookmeyer and Crowley, 1982) method.	Safety Analysis Set
Progression Free Survival Radiographic	The median and other percentiles as appropriate, will be presented using the Kaplan-Meier curve and 95% CI using the Brookmeyer and Crowley (Brookmeyer and Crowley, 1982) method.	Safety Analysis Set
PSA Response (30%, 50%, 70%, and 90%)	The proportion of subjects with PSA response (≥ 30%, ≥ 50%, ≥ 70%, and ≥ 90% decrease from baseline) and 95% CI calculated by Clopper and Pearson method (Clopper and Pearson, 1934) will be reported. Waterfall plot for maximum percent decrease from baseline PSA will be presented.	PSA Response Evaluable Analysis Set PSA Response Evaluable analysis set and applicable to all subjects with a measurable baseline PSA and at least one post-baseline measurable PSA assessment
6-month landmark rPFS	**A 6 month landmark rPFS will be provided as a 6 month estimate of rPFS.**	Safety Analysis Set
Time to PSA Progression	The median and other percentiles as appropriate, will be presented using the Kaplan-Meier curve and 95% CI using the Brookmeyer and Crowley (Brookmeyer and Crowley, 1982) method.	Safety Analysis Set

Endpoint	Statistical Analysis	Analysis Set
Time to Radiographic Progression	The median and other percentiles as appropriate, will be presented using the Kaplan-Meier curve and 95% CI using the Brookmeyer and Crowley (Brookmeyer and Crowley, 1982) method.	Safety Analysis Set
Duration of Response per RECIST 1.1	Descriptive statistics will be presented. If more than 10 subjects experience a Radiographic response, then the following will be done. The median and other percentiles as appropriate, will be presented using the Kaplan-Meier curve and 95% CI using the Brookmeyer and Crowley (Brookmeyer and Crowley, 1982) method.	RECIST 1.1 Evaluable Analysis Set – Objective Responders
Duration of Response PSA50	Descriptive statistics will be presented. If more than 10 subjects experience a PSA response (PSA50), then the following will be done. The median and other percentiles as appropriate, will be presented using the Kaplan-Meier curve and 95% CI using the Brookmeyer and Crowley (Brookmeyer and Crowley, 1982) method.	PSA Response Evaluable Analysis Set – PSA Responders
Time to Symptomatic Skeletal Events	Descriptive statistics will be presented. If more than 10 subjects experience a Symptomatic Skeletal events, then the following will be done. The median and other percentiles as appropriate, will be presented using the Kaplan-Meier curve and 95% CI using the Brookmeyer and Crowley (Brookmeyer and Crowley, 1982) method.	Safety Analysis Set

9.5.3 Analyses of Exploratory Efficacy Endpoint

The analysis of exploratory efficacy endpoints are defined in Table 9-2.

Table 9-2. Exploratory Efficacy Endpoints Summary Table

Endpoint	Statistical Analysis
[redacted]	
Incidence of anti-AMG 340 antibody formation	If available, the incidence and percentage of subjects who develop binding anti-AMG 340 antibodies at any time will be tabulated by planned dose level.

9.6 Safety Analyses

9.6.1 Analyses of Primary Safety Endpoints

Table 9-3. Safety Endpoint Summary Table

Endpoint	Statistical Analysis Method	Analysis Set
Dose Limiting Toxicities (DLTs)	Subject incidence of DLT will be tabulated by planned dose level. A table of DLTs will be provided.	DLT Evaluable Analysis Set

9.6.2 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 25.**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 and treatment-related adverse events will be tabulated by system organ class, preferred term and CTCAE grade. Tables of fatal adverse events, serious adverse events and adverse events leading to withdrawal of AMG 340 by system organ class and preferred term **will be summarized**.

The severity of each adverse event will be graded using CTCAE version 5.0 with the exception of CRS, TLS, and ICANS.

CRS must be graded as per ASTCT referenced by Lee et al, 2019, TLS must be graded using the criteria referenced by Coiffier et al, 2008 and ICANS must be graded by using the criteria referenced by Lee et al, 2019.

The adverse events of interest (CRS) will be summarized by preferred term and worst grade.

9.6.3 Laboratory Test Results

Clinical laboratory data will be reviewed and selected laboratory parameters of interest may be plotted. Depending on the size and scope of changes in laboratory data, the analyses of safety laboratory endpoints may include summary statistics over time and/or changes from baseline over time. Shifts in grades of safety laboratory values from baseline for selected laboratory values may also be provided.

9.6.4 Vital Signs

Vital signs data will be reviewed for each subject. The analyses of vital signs for every subject will include summary statistics over time and/or changes from baseline over time will be provided.

ECOG performance status scores will be summarized for each treatment group at each assessed timepoints. Shifts in scores for ECOG performance status scores between baseline and each assessed timepoint will be tabulated.

9.6.5 Physical Measurements

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

9.6.6 Electrocardiogram

The electrocardiogram (ECG) measurements from this clinical study were performed as per standard of care for routine safety monitoring, rather than for purposes of assessment of potential QT interval corrected (QTc) effect. Since these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data; summaries and statistical analyses of ECG measurements are not planned, and these data would not be expected to be useful for meta-analysis with data from other trials.

9.6.7 Antibody Formation

The incidence and percentage of subjects who develop anti-AMG 340 antibodies at any time will be tabulated overall and by planned dose level.

9.6.8 Exposure to Investigational Product

Details of AMG 340 administration will be listed for every subject. A listing of unique manufacturing lot numbers and a listing of the subjects administered each manufacturing lot number will be provided.

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

Descriptive statistics of the duration of usage, number of cycles, **cumulative (total) dose**, **duration of exposure (months)**, number and percentage of subjects with dose modifications and interruptions will be described.

9.6.9 Exposure to Other Protocol-required Therapy

All other protocol-required therapies, including dexamethasone, diphenhydramine, acetaminophen, ranitidine, and tocilizumab (or siltuximab if tocilizumab is not available) that are commercially available are not provided by Amgen (except if required by local regulation).

Descriptive statistics of total dose (mg) will be produced to describe the exposure to dexamethasone, tocilizumab, and siltuximab.

Subject-level data may be provided instead of the summary if the subject incidence is low or single dose is given.

9.6.10 Exposure to Concomitant Medication

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

9.7 Other Analyses

9.7.1 Analyses of Pharmacokinetic or Pharmacokinetic/[redacted] Endpoints

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

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

PK parameters will include, but are not limited to, maximum observed concentration (C_{max}), time to maximum concentration (t_{max}) and area under the serum concentration-time curve (AUC). Other PK parameters such as clearance and terminal half-life ($t_{1/2}$) may be analyzed. Pharmacokinetic parameters will be estimated using standard non-compartmental approaches based on the PK Analysis Set and summarized by dose

level using descriptive statistics including, but not limited to means, standard deviations, medians, minimums, and maximums. Additional analyses will be performed if useful and appropriate. [redacted]

10. Changes From Protocol-specified Analyses

Analyses for adverse events related to other protocol required therapies will not be provided for part A of the study since this data was not collected in the eCRF. If we do not proceed with Arm B of the study, the primary analysis will be combined with the final analysis.

11. Literature Citations / References

Brookmeyer R, Crowley J. A Confidence Interval for the Median Survival Time. *Biometrics*. 1982;38(1):29-41.

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

Coiffier B, Altman A, Pui CH, Younes A, Cairo MS. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. *J Clin Oncol*. 2008;26:2767-2778.

Kalbfleisch JD, Prentice RL. *The statistical analysis of failure time data*. John Wiley & Sons, New York; 1980.

Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood*. 2014;124:188-195.

Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. *Biol Blood Marrow Transplant*. 2019;25(4):625-638.

Scher HI, Morris MJ, Stadler WM, et al. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. *J Clin Oncol*. 2016;34(12):1402.

Thall PF, Simon RM, Estey EH. Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes. *Statist Med*. 1995;14:357-379.

12. Prioritization of Analyses

There is no prioritization of analyses.

13. Data Not Covered by This Plan

Exploratory data not included in this plan may be analyzed later or may be analyzed by a different Amgen department.

14. Appendices

[redacted]

Appendix B. RECIST 1.1 Assessment and Radiographic Progression

The objective response (OR) and best overall response (BOR) will be derived as per RECIST 1.1. Radiographic progression will be derived as per RECIST 1.1 with PCWG3 modifications.

[redacted]

Table 14-1. Confirmed BOR per RECIST 1.1 where Confirmation of CR/PR is Required

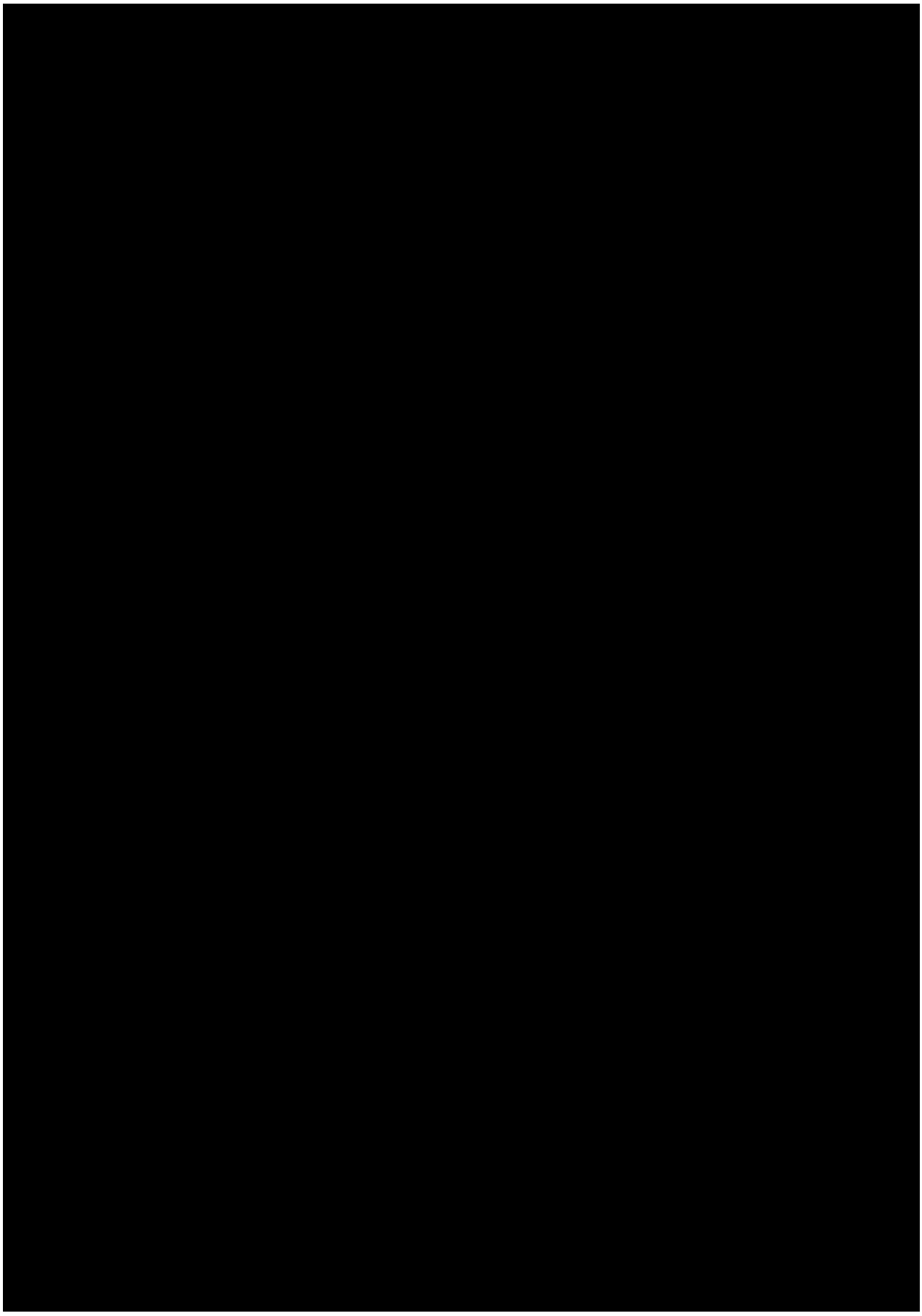
Criterion	Time point T1 Response	T1 ≥ 35 days after Baseline?	Time point T2 Response	T2 ≥ 35 days after Baseline?	T2 ≥ 28 days after T1?	Confirmation
C1	CR	Yes	CR	-	Yes	CR
C2			CR	-	No	SD
C3			PR, SD	-	-	Query data*
C4			PD	-	-	SD
C5			NE, No further evaluations			SD
C6		No	CR	-	Yes	CR
C7			CR	Yes	No	SD
C8			PR, SD	-	-	Query data*
C9			PD	-	-	PD
C10			NE, No further evaluations			NE
C11	PR	Yes	CR, PR	-	Yes	PR

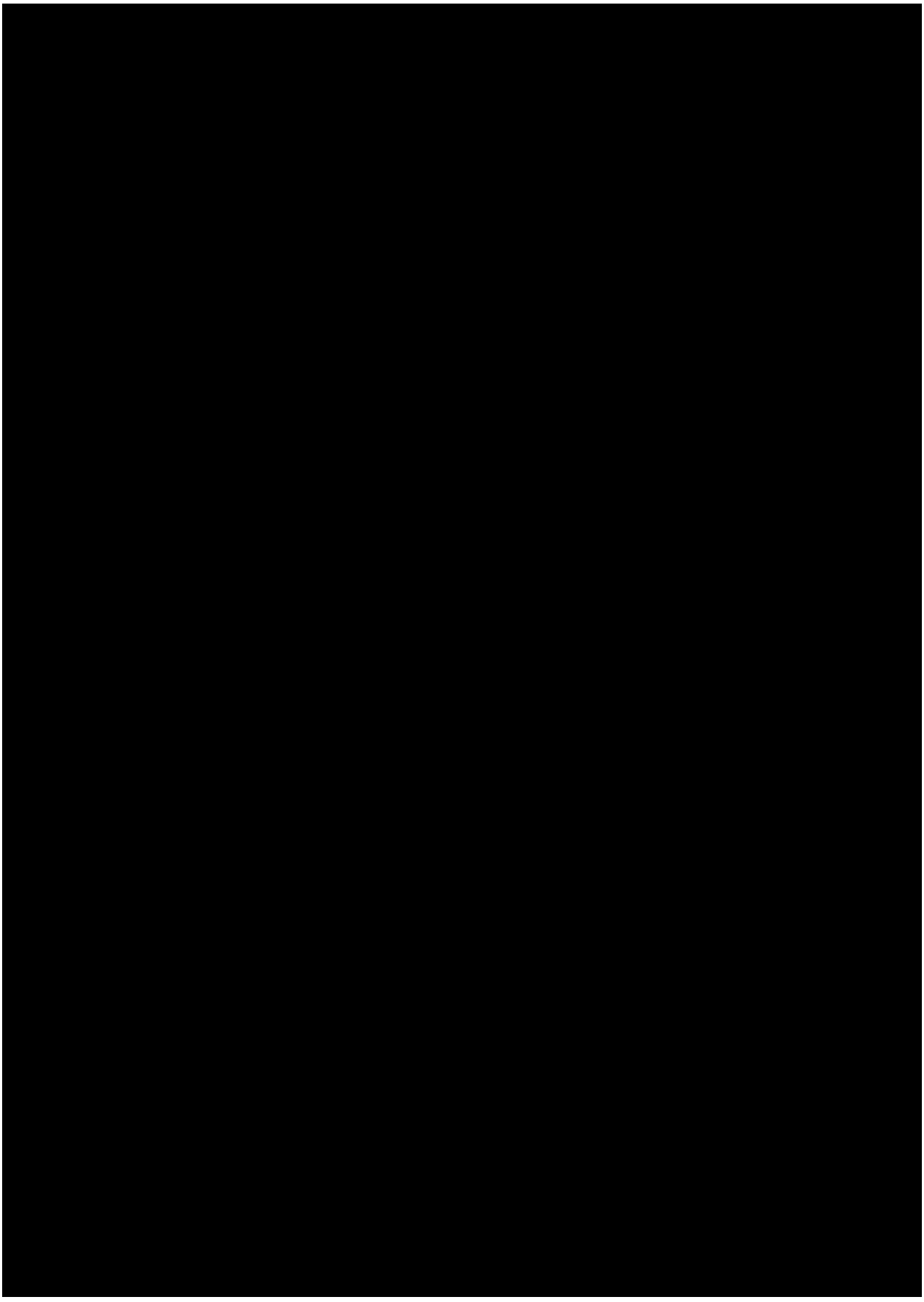
C12			CR, PR	-	No	SD
C13			SD	-	-	SD
C14			PD	-	-	SD
C15			NE, No further evaluations			SD
C16		No	CR, PR	-	Yes	PR
C17			CR, PR	Yes	No	SD
C18			SD	Yes	-	SD
C19			PD	-	-	PD
C20			NE, No further evaluations			NE
C21	SD	Yes	CR, PR, SD, PD, NE, no more evaluation			SD
C22		No	CR, PR, SD	Yes	-	SD
C23			CR, 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 subsequent timepoint, 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 (35 days) 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. If this response sequence occurs in the dataset, a data issue needs to be raised and resolved.

Note: T1 could be any time point on study (best response) and does not necessarily indicate the first on-treatment scan.





[redacted]

Table 14-3. Bone Progression Status as per PCWG3

Bone Lesion Response	Definition
NEB	No evidence of Bone Lesion at screening.
NE (Not Evaluable)	No evaluable bone scan is available (i.e., not performed or issue with the quality of image) at that visit.
Non-PD	(1) For the first post-treatment bone scan (e.g., Week 8), if appearance of <2 new lesions relative to screening/baseline, then set to Non-PD. (2) For scans after the first post-treatment scan, if appearance <2 new lesions relative to the first post-treatment scan, then set to Non-PD.
PDu (Unconfirmed PD)	(1) For the first post-treatment bone scan (e.g., Week 8), if appearance of ≥2 new lesions relative to screening/baseline, then set to PDu. (2) For scans after the first post-treatment scan, if appearance ≥2 new lesions relative to the first post-treatment scan, then set to PDu.
PDc (Confirmed PD)	(1) For the first post-treatment bone scan (e.g., Week 8), if appearance of ≥2 new lesions relative to screening/baseline and confirmed by the appearance of ≥2 additional new lesions at the next scan date, then set to PDc. (2) For scans after the first post-treatment scan, if appearance ≥2 new lesions relative to the first post-treatment scan and confirmed by the persistence of these new lesions at the next scan date, then set to PDc.

Bone lesion status (Absent/Present) will be marked as follows:

Bone Lesion (Present/Absent)	Definition
Absent	Total number of lesions related to metastatic disease for the specific timepoint is 0.
Present	Total number of lesions related to metastatic disease for the specific timepoint is more than 0.

[redacted]

Table 14-4. Radiographic Progression by RECIST 1.1 with PCWG3 Modifications

RECIST 1.1 visit response (soft tissue/visceral)[a]	Bone Progression Status	Bone Lesion (Present/Absent)	Radiographic Progression by RECIST 1.1 with PCWG3 Modification
PD	Any	Any	PD
Any[d]	PDc	Any	PD[b]
Any except PD	PDu	Any	Non-PD
NE	Non-PD, NEB, or NE	Any	NE
SD	Non-PD, NEB, or NE	Any	Non-PD
Non-CR/Non-PD[c]	Non-PD, NEB, or NE	Any	Non-PD
PR	Non-PD, NEB, or NE	Any	Non-PD
CR	Non-PD, NEB, or NE	Any	Non-PD

NED	NE	Any	NE
NED	Non-PD	Any	Non-PD
NED	NEB	Any	NED

CR = Complete Response; PR = Partial Response; SD = Stable Disease; PD = Progressive Disease; NE = Not Evaluable (if a scan is not performed at that visit, it will be considered NE); NEB = No Evidence of Bone Lesion at screening; NED = No Evidence of Disease (only relevant if there were no target lesions and non-target lesions at all visits), 'Undefined' in vendor data.

[a] Collected time point responses

[b] Following the confirmation of PD at the subsequent bone scan, the overall radiological visit response of progression for the visit will be programmatically derived as PD using the progression date (previous bone scan date where new lesion first seen) captured on the eCRF

[c] For subjects with non-measurable disease only at baseline.

[d] For subjects with RECIST 1.1 response of CR, PR, SD, PD, NE or Missing.

Appendix C. Additional Definitions

Information described below will be reported from eCRF

Partial Response (PR) per RECIST 1.1:

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-Partial Response (non-PR)/non-Progressive Disease (non-PD).

Complete Response (CR) per RECIST 1.1:

The 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.

Progressive Disease (PD) per RECIST 1.1:

At least 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD) per RECIST 1.1:

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

Non-CR/Non-PD per RECIST 1.1:

Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits. This time point visit response is only valid for subjects who do not have measurable disease per RECIST 1.1 at baseline.

Measurable baseline disease per RECIST 1.1:

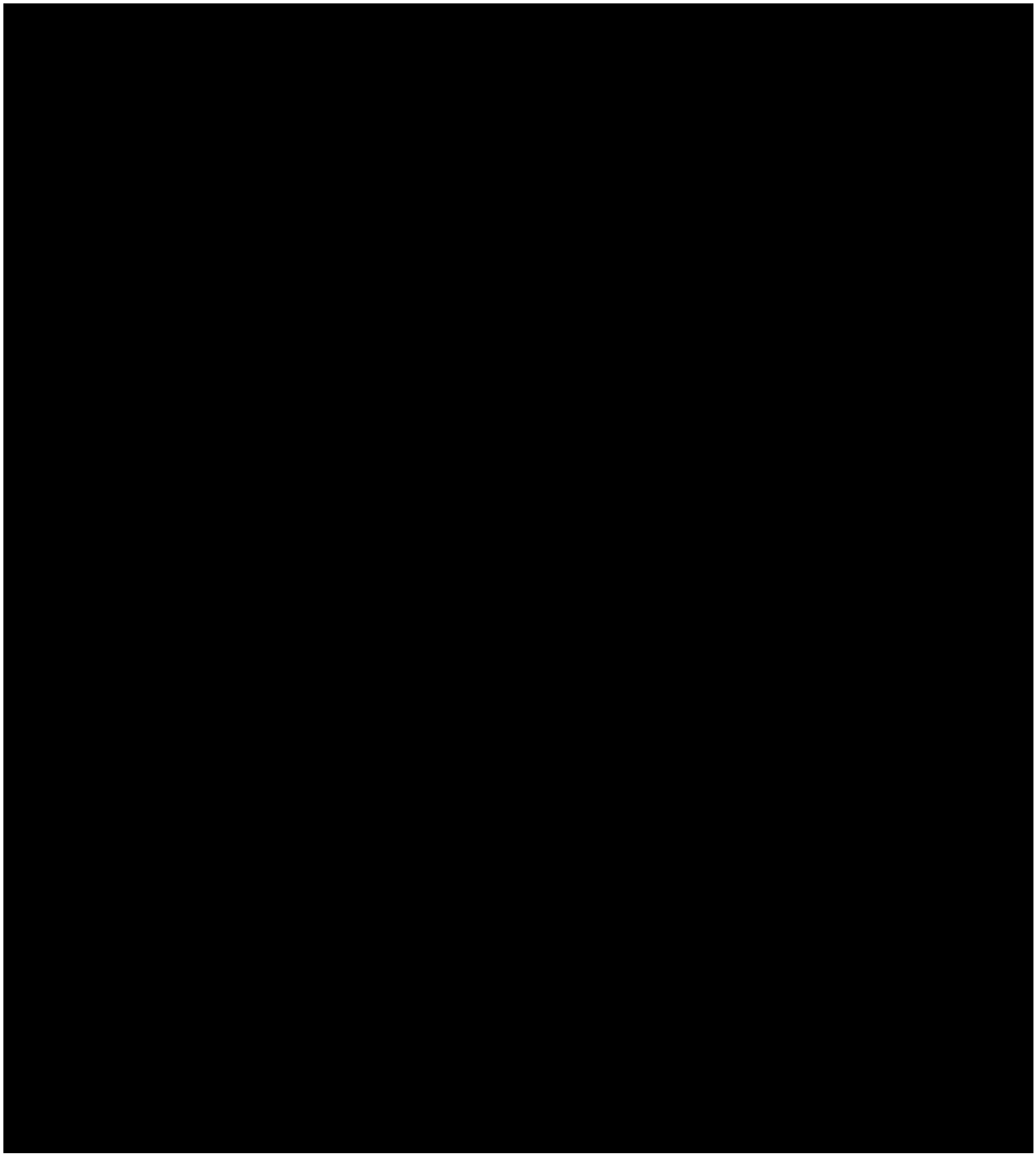
Measurable baseline disease is defined as “Lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of 10 mm by CT/MRI. To be measurable a lymph node must be ≥ 15 mm in short axis when assessed by CT/MRI. All tumor measurements must be recorded in millimeters. Note: Previously irradiated lesions are non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.”

Evaluable tumor assessment per RECIST 1.1:

Either of the following assessment must be performed for an evaluable tumor assessment (on or before subsequent anti-cancer therapy):

- CT/MRI scan to assess tumor response per RECIST 1.1
- Bone scan to assess bone disease progression status

The results must be adequate to define a visit response, i.e., a visit overall response other than not evaluable (NE) for RECIST 1.1.



Appendix D. Censoring Rules

Censoring rules for radiographic PFS (rPFS):

Situation up to DCO/EOS	Date of Event or Censoring	Outcome
No evaluable post-baseline or on-study disease assessment; on study without disease progression or death recorded	Date of the first dose of Investigational product (AMG 340)	Censored
PD prior to new anti-cancer therapy	Date of PD	Event
No PD, but death recorded without new anti-cancer therapy	Date of Death	Event
Start of new anti-cancer therapy prior to PD or death, or prior to any other disease assessment if there is no PD or death recorded	Date of last evaluable radiographic tumor assessment prior to the start of new anti-cancer therapy	Censored
No PD or death, no new anti-cancer therapy	Date of last evaluable radiographic tumor assessment	Censored

DCO: Data Cut-off; EOS: End of Study; PD: Progressive Disease

Censoring rules for PSA PFS:

Situation up to DCO/EOS	Date of Event or Censoring	Outcome
No evaluable post-baseline or on-study PSA assessment (on study without PSA progression or death); no evaluable baseline PSA assessment	Date of the first dose of Investigational product (AMG 340)	Censored
PSA Progression	Date of PSA Progression	Event
Death	Date of Death	Event

All other scenarios	Date of last PSA assessment.	Censored

DCO: Data Cut-off; EOS: End of Study; PSA: Prostate Specific Antigen

Censoring rules for Time to PSA Progression:

Situation up to DCO/EOS	Date of Event or Censoring	Outcome
No evaluable baseline or post-baseline or on-study PSA assessment	Date of the first dose of Investigational product (AMG 340)	Censored
PSA Progression	Date of PSA Progression	Event
All other scenarios	Date of last PSA assessment	Censored

DCO: Data Cut-off; EOS: End of Study; PSA: Prostate Specific Antigen

Censoring rules for Time to Radiographic Progression:

Situation up to DCO/EOS	Date of Event or Censoring	Outcome
No evaluable post-baseline or on-study disease assessment; on study without progressive disease or death	Date of the first dose of Investigational product (AMG 340)	Censored
PD prior to new anti-cancer therapy	Date of PD	Event
No PD, but death recorded without new anti-cancer therapy	Date of last evaluable radiographic tumor assessment	Censored
Start of new anti-cancer therapy prior to PD or death, or prior to any other disease assessment if there is no PD or death recorded	Date of last evaluable radiographic tumor assessment prior to the start of new anti-cancer therapy	Censored
No PD or death, no new anti-cancer therapy	Date of last evaluable radiographic tumor assessment	Censored

DCO: Data Cut-off; EOS: End of Study; PD: Progressive Disease

Censoring rules for DOR per RECIST 1.1 (CT/MRI assessment):

- Data for responders who are alive and without disease progression or new anti-cancer therapy are censored at the time of last evaluable tumor assessment by CT/MRI scan.
- Data for responders who are alive and without disease progression but who started new anti-cancer therapy are censored at the time of last evaluable tumor assessment by CT/MRI scan before the start of new anti-cancer therapy.

Situation up to DCO/EOS	Date of Event or Censoring	Outcome
PD prior to new anti-cancer therapy	Date of PD	Event
No PD, but death recorded without new anti-cancer therapy	Date of Death	Event
Start of new anti-cancer therapy prior to PD or death, or prior to any other disease assessment if there is no PD or death recorded	Date of last evaluable tumor assessment by CT/MRI prior to the start of new anti-cancer therapy	Censored
No PD or death, no new anti-cancer therapy	Date of last evaluable tumor assessment by CT/MRI	Censored

DCO: Data Cut-off; EOS: End of Study; PD: Progressive Disease

Censoring rules for PSA Duration of Response:

Situation up to DCO/EOS	Date of Event or Censoring	Outcome
PSA progression after PSA response (PSA50).	Date of PSA progression.	Event
Death after PSA response (PSA50).	Date of Death.	Event
All other scenarios	Date of last PSA assessment.	Censored

DCO: Data Cut-off; EOS: End of Study; PSA: Prostate Specific Antigen