Statistical Analysis Plan

Protocol Title:	A Phase 1 Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Prostate Specific Membrane Antigen Half-life Extended Bispecific T-cell Engager AMG 160 in Subjects With Metastatic Castration-resistant Prostate Cancer
Short Protocol Title:	A Phase 1 Study of AMG 160 in Subjects With Metastatic Castration-resistant Prostate Cancer
Protocol Number:	20180101
NCT Number:	NCT03792841
Authors:	[redacted]
Sponsor:	Amgen Inc. One Amgen Center Drive Thousand Oaks, CA 91320
SAP Date:	**Document Version** — **Date** **Original (v [1.0])** — 19 March 2019 **Amendment [1 (V2.0)]** — 11 June 2021 **Amendment [2 (V3.0)]** — 08 October 2021 **Amendment [3 (V4)]** — 08 July 2022 **Amendment [4 (V5)]** — 20 September 2022

Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	19MAR2019	Original SAP
Amendment 1 (V2.0)	11JUN2021	• Updated to align with protocol amendment 8 • Updated definition of CTC response and conversion. • Updated definition of PSA progression, radiographic progression and updated censoring rule in radiographic

		progression-free survival, PSA progression-free survival, radiographic progression, duration of radiographic response, time to radiographic progression and time to PSA progression. • Updated definition of RECIST Evaluable and PSA Response Analysis Set • Updated section of Handling of Missing data and Electrocardiogram. • Added PSA Response Sensitivity Analysis • Added Appendix C, D and E.
Amendment 2 (V3.0)	08OCT2021	• Updated to align with protocol amendment 9 superseding version. • Updated the TEAE definition to remove (+3). • Updated the Treatment-related TEAE definition. • Updated section 5.1.2: o Objective Response (OR) per RECIST 1.1 o Added the definition Duration of Response per RECIST 1.1 to replace radiographic DOR. Also added the censoring rules in the Appendix F o Duration of PSA Response, Time to PSA Progression, PSA PFS: • Added the censoring rules in the Appendix F. • Added the derivation of "Last known alive date". • Updated the definition of SSE. • Updated Sections 7.1, 7.2 and 7.3, appendices A and C.

Amendment 3 (V4)	08JUL2022	• Updated to align with protocol amendment 10. • Updated section 3.1 for part 2 and Figure 2. [redacted] • Updated section 5 by adding a condition if the death date is available and also by adding missing forms under Last known alive date section. • Updated Table 1 in section 9.5 • Updated section 11 to add/remove literature/citations/references. • Updated Appendix C for Interim/Primary Analysis and Final Analysis by adding a text 'the last assessment of subjects'.
Amendment 4 (V4.1)	**20SEP2022**	• **Updated the definition of Baseline to 'the last non-missing value for a given assessment that is on or prior to the first dose of AMG 160 or Pembrolizumab, whichever occurs earlier'.** • **Removed Table 4- RECIST 1.1 (Soft tissue lesions) and updated the numbers for other tables from Appendix C** • **Updated table 5 from step 2 in Appendix C** • **Updated table BOR per RECIST 1.1 table by removing the Non-PD in Appendix C** • **Removed rule of confirmed/unconfirmed PD from RECIST 1.1** • **Added definitions for unconfirmed responses for interim analysis**

		• **Removed text '*Soft-tissue disease progression must be confirmed with a second MRI/CT scan at least 4 weeks later*' from Radiographic progression definition.** • **Added a table of BOR Derivation in Appendix C to derive the confirmed BOR status** • **Step 3 from Appendix C is updated with new step of Unconfirmed responses definitions.**

Table of Contents

Table of Contents 4

1. Introduction 11

2. Objectives, Endpoints and Hypotheses 11
   - 2.1 Objectives and Endpoints 11
   - 2.2 Hypotheses and/or Estimations 14

3. Study Overview 14
   - 3.1 Study Design 14
   - 3.2 Sample Size 24
   - 3.3 Adaptive Design 25

4. Covariates and [redacted] 26
   - 4.1 Planned Covariates 26

[redacted]

5. Definitions 26
   - 5.1 Study Endpoints 26
     - 5.1.1 Primary Endpoints Definitions 27
     - 5.1.2 Secondary Endpoints Definitions 27
     - 5.1.3 Exploratory Endpoints Definitions 33
   - 5.2 Study Time Points 34
   - 5.3 Demographics and Baseline Related Definitions 35

6. Analysis Sets 36
   - 6.1 Safety Analysis Set 36
   - 6.2 Pharmacokinetic/Pharmacodynamic Analyses Set(s) 36
   - 6.3 Study-specific Analysis Sets 36
     - 6.3.1 RECIST 1.1 Evaluable Analysis Set 36
     - 6.3.2 PSA Response Evaluable Analysis Set 36
     - 6.3.3 CTC Evaluable Analysis Set 36
     - 6.3.4 CTC Conversion Analysis Set 37
     - 6.3.5 DLT Evaluable Analysis Set 37

7. Planned Analyses 37
   - 7.1 Interim Analysis and Early Stopping Guidelines 37

[redacted]

   - 7.2 Primary Analysis 39
   - 7.3 Final Analysis 39

8. Data Screening and Acceptance 39
   - 8.1 General Principles 39
   - 8.2 Data Handling and Electronic Transfer of Data 39
   - 8.3 Handling of Missing and Incomplete Data 40

8.4 Detection of Bias 40
8.5 Outliers 40
8.6 Distributional Characteristics 40
8.7 Validation of Statistical Analyses 41

9. Statistical Methods of Analysis 41
9.1 General Considerations 41
9.2 Subject Accountability 41
9.3 Important Protocol Deviations 41
9.4 Demographic and Baseline Characteristics 41
9.5 Efficacy Analyses 43
9.6 Safety Analyses 50
9.6.1 Analyses of Primary Safety Endpoint(s) 50
9.6.2 Adverse Events 51
9.6.3 Laboratory Test Results 52
9.6.4 Vital Signs 52
9.6.5 Physical Measurements 52
9.6.6 Electrocardiogram 52
[redacted]
9.6.8 Exposure to Investigational Product 53
9.6.9 Exposure to Other Protocol-required Therapy 53
9.6.10 Exposure to Concomitant Medication 53
9.7 Other Analyses 53
9.7.1 Analyses of Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Endpoints 53
[redacted]

10. Changes From Protocol-specified Analyses 54

11. Literature Citations / References 54

12. Prioritization of Analyses 55

13. Data Not Covered by This Plan 55

14. Appendices 56
[redacted]
Appendix B. Code Fragments 58
Appendix C. RECIST 1.1 Assessment and Radiographic Progression 59
Appendix D. Modified Toxicity Probability Interval Design (mTPI-2) 67
Appendix E. Additional Definition 68
Appendix F. Censoring Rules 69

List of Tables

Table 1. Secondary Efficacy Endpoint Summary Table 42
Table 2. Exploratory Efficacy Endpoint Summary Table 49
Table 3. Safety Endpoint Summary Table 49
Table 4. Confirmed BOR per RECIST 1.1 where Confirmation of CR/PR is Required....60
[redacted]
Table 7. Radiographic Progression by RECIST 1.1 with PCWG-3....65

List of Figures

Figure 1. Parts 1, [redacted] Study Schema 19
Figure 2. Part 2 Study Schema....20
Figure 3. Part 3 Study Schema....21
Figure 4. Part 6 Study Schema....22

List of Abbreviations

Abbreviation or Term	Definition/Explanation
ADR	adverse drug reaction
ADT	androgen-deprivation therapy
AE	adverse event
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
ALP	alkaline phosphatase
[redacted]	
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{last}	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
BID	twice daily
BIL	bilirubin
BiTE	bispecific T-cell engager
BLRM	Bayesian logistic regression model
[redacted]	
CD	cluster of differentiation
CFR	US Code of Federal Regulations
C_{max}	maximum serum concentration
C_{min}	minimum serum concentration
CNS	central nervous system
CR	complete response
CRF	case report form
CRS	cytokine release syndrome
CT	computed tomography
CTC(s)	circulating tumor cell(s)
CTC0	CTC-response
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	
DILI	drug-induced liver injury
DLRM	Dose Level Review Team Meeting
DLRT	Dose Level Review Team
DLT	dose-limiting toxicities
DOR	duration of response
EC_{50}	half maximal effective concentration
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic CRF

Abbreviation or Term	Definition/Explanation
EDC	electronic data capture
eIV	extended intravenous
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
EOI	end of infusion
[redacted]	
EU	European Union
[redacted]	
Fc	fragment crystallizable
FDG PET/CT	fluorodeoxyglucose PET/CT
FFPE	formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GnRH	gonadotropin-releasing hormone
HLE	half-life extended
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
INR	international normalized ratio
IPIM	Investigational Product Instruction Manual
IRB	Institutional Review Board
IV	intravenous
IVSS	intravenous solution stabilizer
JAK	janus kinase
LDH	lactate dehydrogenase
LHRH	lutenizing hormone-releasing hormone agonist
LTFU	long-term follow-up
MABEL	minimum anticipated biological effect
mCRPC	metastatic castration-resistant prostate cancer
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA scan	multigated acquisition scan

Abbreviation or Term	Definition/Explanation
NCT	National Clinical Trials
OR	objective response
OS	overall survival
PCWG3	Prostate Cancer Working Group 3
PD	pharmacodynamics
PDE4	phosphodiesterase-4
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PO	orally
PR	partial response
PSA	prostate-specific antigen
PSMA	prostate specific membrane antigen
Q2W	every 2 weeks
[redacted]	
QD	once daily
RP2D	recommended phase 2 dose
RECIST	Response Evaluation Criteria in Solid Tumors
[redacted]	
scFc	single chain fragment crystallizable
SFU	safety follow-up
Source Data	information from an original record or certified copy of the original record containing subject information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
TBL	total bilirubin
TLS	tumor lysis syndrome
TNFα	tumor necrosis factor alpha
TPI	toxicity probability interval
ULN	upper limit of normal
US	United States
USPSTF	US Preventive Services Task Force
WFI	water for injection

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 **10** for study 20180101, AMG 160 dated **16 March 2022**. The scope of this plan includes the analysis that is 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

Parts 1, 3, [redacted] and 6: AMG 160 monotherapy	
Objectives	**Endpoints**
Primary	
• Evaluate the safety and tolerability of AMG 160 in adult subjects • Part 1 only: Determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D)	• dose-limiting toxicities (DLTs) • treatment-emergent adverse events • treatment-related adverse events • changes in vital signs, electrocardiogram (ECG), and clinical laboratory tests
Secondary	
• Characterize the pharmacokinetics (PK) of AMG 160	• PK parameters for AMG 160 following intravenous (IV) administration including but not limited to maximum serum concentration (C_{max}), minimum serum concentration (C_{min}), area under the concentration-time curve (AUC) over the dosing interval, accumulation following multiple dosing, and, if feasible, half-life ($t_{1/2}$)
• Evaluate preliminary anti-tumor activity of AMG 160	• objective response (OR) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 • prostate-specific antigen (PSA) response (30%, 50%, 70%, 90%) • duration of response (DOR) (per RECIST 1.1) • PSA DOR based on PSA50 response • ^{68}Gallium (^{68}Ga)-prostate-specific membrane antigen (PSMA)-11 positron emission tomography (PET)/computed tomography (CT) and ^{18}F-fluorodeoxyglucose (FDG) PET/CT based response evaluation (Parts [redacted] and 6 are not included) • time to progression (radiographic and PSA) • progression-free survival (PFS) (radiographic and PSA) • 1, 2, and 3-year overall survival (OS)

	• circulating tumor cells (CTCs) – response (CTC0) and rate of CTC conversion • other Prostate Cancer Working Group 3 (PCWG3)-recommended endpoints (time to symptomatic skeletal events, alkaline phosphatase [total, bone], lactate dehydrogenase [LDH], hemoglobin, neutrophil-to-lymphocyte ratio, urine N-telopeptide)
• Part 6 only: Evaluate the effect of co-administration of multiple dosing of AMG 160 on plasma exposures of specific probes of CYP enzymes	• PK parameters of specific probes of CYP enzymes including, but not limited to, C_{max}, area under the concentration-time curve over a 24-hour period (AUC24) and, if feasible, $t_{1/2}$
Part 2: AMG 160 in combination with pembrolizumab	
Objectives	**Endpoints**
Primary	
• Evaluate the safety and tolerability of AMG 160 in combination with pembrolizumab in adult subjects • Determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) of AMG 160 in combination with pembrolizumab	• dose-limiting toxicities (DLTs) • treatment-emergent adverse events • treatment-related adverse events • changes in vital signs, electrocardiogram (ECG), and clinical laboratory tests
Secondary	
• Characterize the pharmacokinetics (PK) of AMG 160 in combination with pembrolizumab	• PK parameters for AMG 160 following intravenous (IV) administration including but not limited to maximum serum concentration (C_{max}), minimum serum concentration (C_{min}), area under the concentration-time curve (AUC) over the dosing interval, accumulation following multiple dosing, and, if feasible, half-life ($t_{1/2}$)
• Evaluate preliminary anti-tumor activity of AMG 160 in combination with pembrolizumab	• objective response (OR) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 • prostate-specific antigen (PSA) response (30%, 50%, 70%, 90%) • duration of response (DOR) (per RECIST 1.1) • PSA DOR based on PSA50 response • ^{68}Gallium (^{68}Ga)-prostate-specific membrane antigen (PSMA)-11 positron emission tomography (PET)/computed tomography (CT) and ^{18}F-fluorodeoxyglucose (FDG) PET/CT based response evaluation • time to progression (radiographic and PSA) • progression-free survival (PFS) (radiographic and PSA) • 1, 2, and 3-year overall survival (OS)

	• circulating tumor cells (CTCs) – response (CTC0) and CTC conversion • other Prostate Cancer Working Group 3 (PCWG3)-recommended endpoints (time to symptomatic skeletal events, alkaline phosphatase [total, bone], lactate dehydrogenase [LDH], hemoglobin, neutrophil-to-lymphocyte ratio, urine N-telopeptide)

Parts 1, 3, [redacted]	
Objectives	**Endpoints**
Exploratory	
[redacted]	

Part 2: AMG 160 in combination with pembrolizumab	
Objectives	**Endpoints**
Exploratory	
[redacted]	



2.2 Hypotheses and/or Estimations

AMG 160 monotherapy and in combination with pembrolizumab will demonstrate acceptable safety and tolerability in subjects with mCRPC at 1 or more dose levels with at least 1 dose level showing preliminary evidence of anti-tumor activity. No formal hypotheses will be tested.

3. Study Overview

3.1 Study Design

Part 1: AMG 160 Monotherapy

Part 1 is an open-label, ascending, multiple dose, phase 1 study evaluating AMG 160 administered as a short-term IV infusion (approximately 60 minutes) every 2 weeks in a 28-day cycle in subjects with mCRPC (up to 190 subjects). To reduce the incidence of CRS, the cycle 1 dosing schedule may be adapted to include an alternate dosing schedule involving a planned 3-day eIV infusion (with the option to modify to range from 2-day to 7-day infusion) within the first week of cycle 1 followed by target doses (short-term IV infusions).

The study will consist of:

- dose-exploration phase (Protocol section 7.4.1.1)
- dose-expansion phase (1a and 1b) (Protocol section 7.4.1.2)

The dose-exploration phase of the study will estimate the MTD of AMG 160 using a Bayesian logistic regression model (BLRM; Neuenschwander et al, 2008). Recommended phase 2 dose (RP2D) may be identified based on emerging safety, efficacy, and pharmacodynamic data prior to reaching an MTD. Alternative dosing schedule(s) may be explored based on emerging PK and safety data.

Following the dose-exploration phase in Part 1, a dose-expansion phase will be conducted in 2 parts (1a and 1b) to confirm safety, PK, and pharmacodynamics at the MTD or RP2D and to obtain further safety and efficacy data [redacted] analysis. Dose expansion 1a will enroll approximately 50 subjects, independent of PSMA status. Dose expansion 1b will enroll approximately 50 subjects [redacted]

During the dose exploration phase, individual cohorts of subjects from [redacted] will be enrolled with a safety lead-in at 1 or more dose levels below the MTD or RP2D followed by evaluation at the MTD or RP2D to confirm the safety, tolerability, MTD and/or RP2D of AMG 160 in [redacted] subjects, respectively.

Additional subjects may be enrolled in 1 or more monotherapy dose levels that have been shown to be safe and tolerable (defined as backfill enrollment). This backfill enrollment will be done to better estimate the RP2D and better characterize the safety, efficacy, PK, and pharmacodynamics for AMG 160 monotherapy and may be concurrent with dose escalation to identify the MTD. Refer to Figure 1.

Part 2: AMG 160 Combination with Pembrolizumab

This combination dose exploration study (n = 30) will explore the safety, pharmacokinetics, and efficacy of AMG 160 in combination with the PD-1 inhibitor Pembrolizumab in approximately 30 subjects with mCRPC.

AMG 160 will be administered as a short-term IV infusion (approximately 60 minutes) every 2 weeks in a 28-day cycle in subjects with mCRPC. The starting dose of AMG 160 will be 1 dose level below the dose level that has been recommended as safe and tolerable by DLRT. To reduce the incidence of CRS, the cycle 1 dosing schedule includes a multi-step dosing schedule (see Section 7.1.1.2 of protocol). Pembrolizumab will be dosed [redacted] on AMG 160 dosing days beginning with the first AMG 160 target dose, and Pembrolizumab infusion will take place after AMG 160 infusion and post-infusion flush. The DLRT may modify the AMG 160 and Pembrolizumab dosing schedule based on emerging safety data.

This dose exploration study will estimate the MTD and/or RP2D of AMG 160 in combination with Pembrolizumab using a modified toxicity probability interval design (mTPI-2; Section12.16 of protocol). Recommended phase 2 dose (RP2D) may be identified based on emerging safety, efficacy, pharmacokinetic, and pharmacodynamic data prior to reaching an MTD. If necessary, 10 additional subjects may be enrolled at

the RP2D for subjects in order to obtain additional safety and pharmacokinetic data. Alternative dosing schedule(s) may be explored based on emerging PK and safety data.

Refer to Figure 2.

Part 3: Etanercept Prophylaxis for AMG 160-related CRS

Part 3 will evaluate the effect of etanercept premedication on the safety, tolerability, and efficacy of AMG 160. Specifically, Part 3 will assess whether prophylaxis with the TNF-α inhibitor etanercept might decrease the frequency and severity of CRS without compromising the efficacy of AMG 160.

In an initial cohort of 6 to 8 subjects, AMG 160 will be administered as described in Part 1 at the MTD, RP2D, or highest dose level deemed safe and tolerable. In addition to dexamethasone prophylaxis, subjects in the cohort will also receive prophylaxis with etanercept ([redacted] prior to each cycle 1 dose of AMG 160.

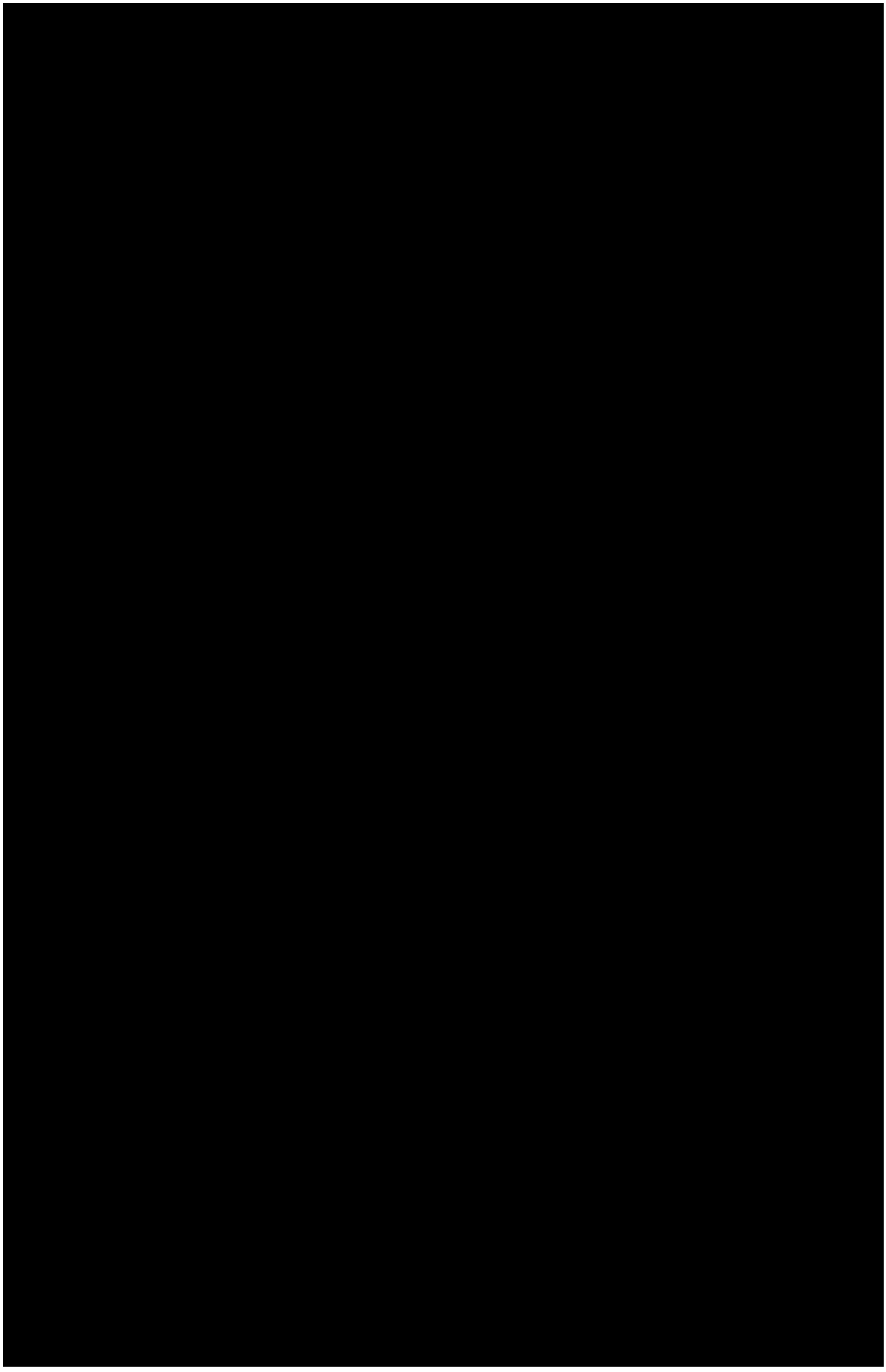
Subject incidence of safety events, including dose-limiting toxicities (DLTs), serious adverse events, and adverse events leading to treatment discontinuation or dose reduction, will be reviewed when at least 3 DLT-evaluable subjects complete the DLT window. If etanercept does not reduce the signs and symptoms of CRS, enrollment in Part 3 will be discontinued.

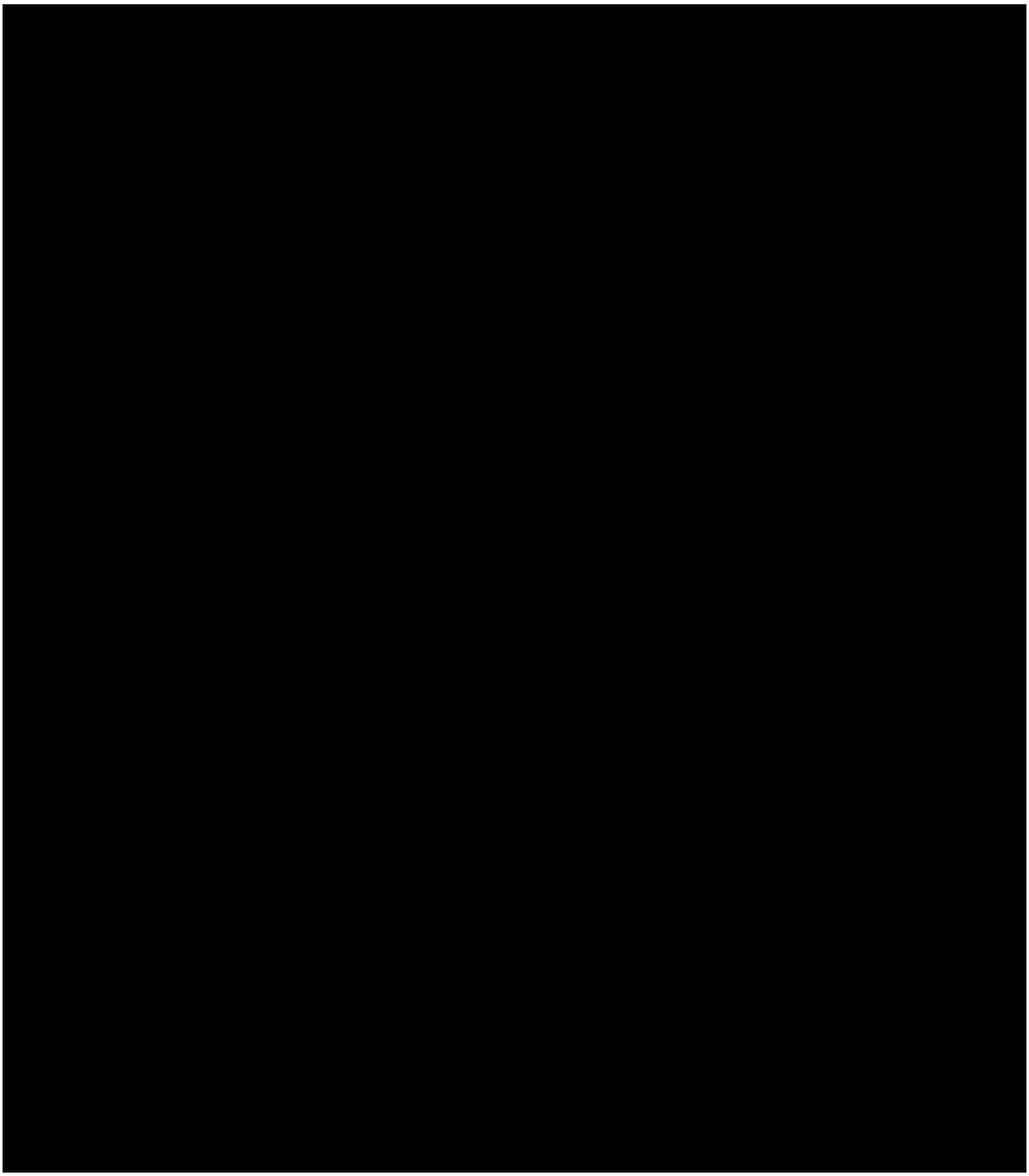
If etanercept prophylaxis reduces signs and symptoms of CRS and improves tolerability of AMG 160 in cohort 1, an additional cohort of 6 to 8 subjects may receive AMG 160 with etanercept prophylaxis only (ie, without dexamethasone premedication) [redacted] prior to each cycle 1 dose of AMG 160. Based on safety data, additional subjects (up to 20 in the cohort) may be enrolled in Part 3 to evaluate the effect of etanercept premedication (with or without dexamethasone premedication) on the safety, tolerability, and efficacy of AMG 160. Refer to Figure 3.

If etanercept reduces signs and symptoms of CRS without impacting efficacy in Part 3, etanercept prophylaxis (with or without dexamethasone prophylaxis) may be added to Parts 1, 2, [redacted]

Part 3 will be conducted in US and Canada only.

[redacted]





Part 6: Cytochrome P450 (CYP) Cocktail Drug Interaction Cohort

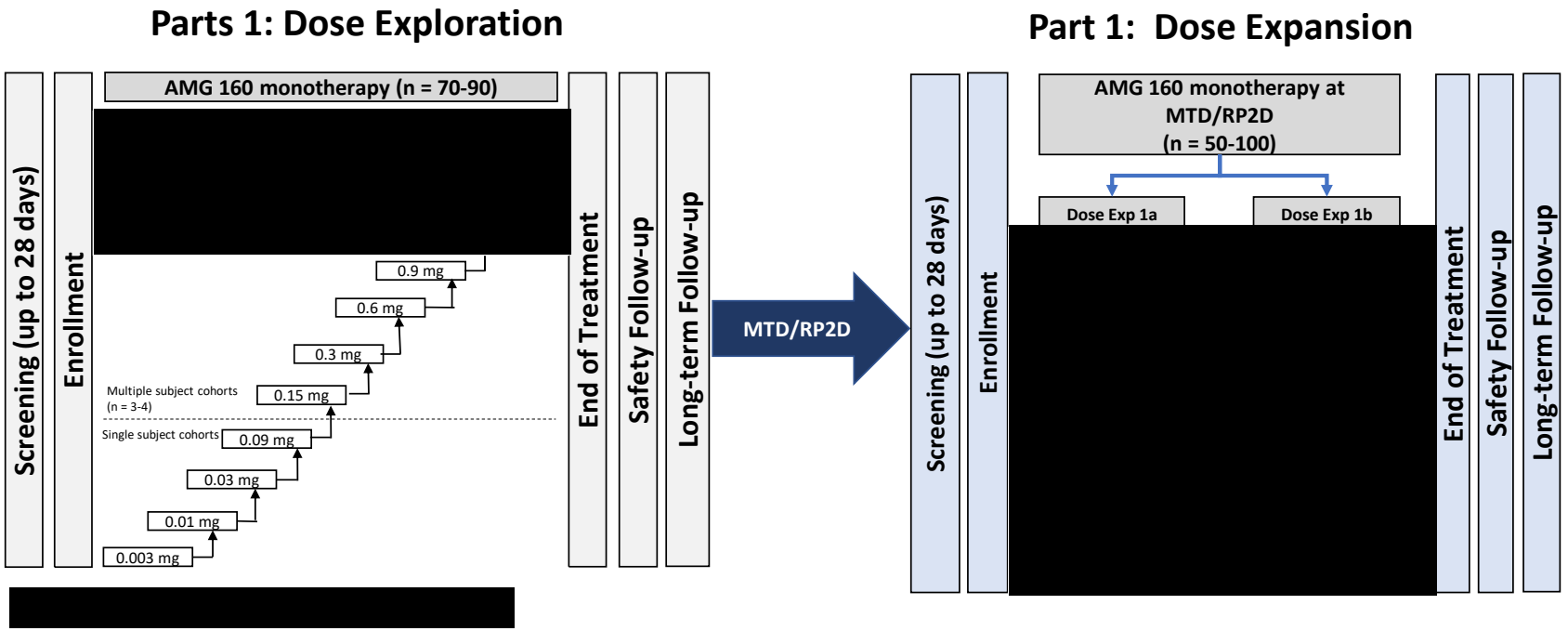
Part 6 of this study will evaluate the effect of co-administration of multiple dosing of AMG 160 on plasma exposures of specific probes of CYP enzymes using a modified Cooperstown 5+1 CYP phenotyping cocktail. Up to 8 subjects are planned to be enrolled. Briefly, each subject will receive a single oral dose of all components of the CYP phenotyping cocktail one day prior to cycle 1 day 1 and subsequently on cycle 2 day 1. AMG 160 will be administered at the MTD/RP2D as determined in Part 1.

Part 6 will be conducted in the US and Singapore. Refer to Figure 4.

The overall study design is described by a study schema. The endpoints are defined in Section 2.1.

Study Schema

Figure 1. Parts 1, [redacted] Study Schema

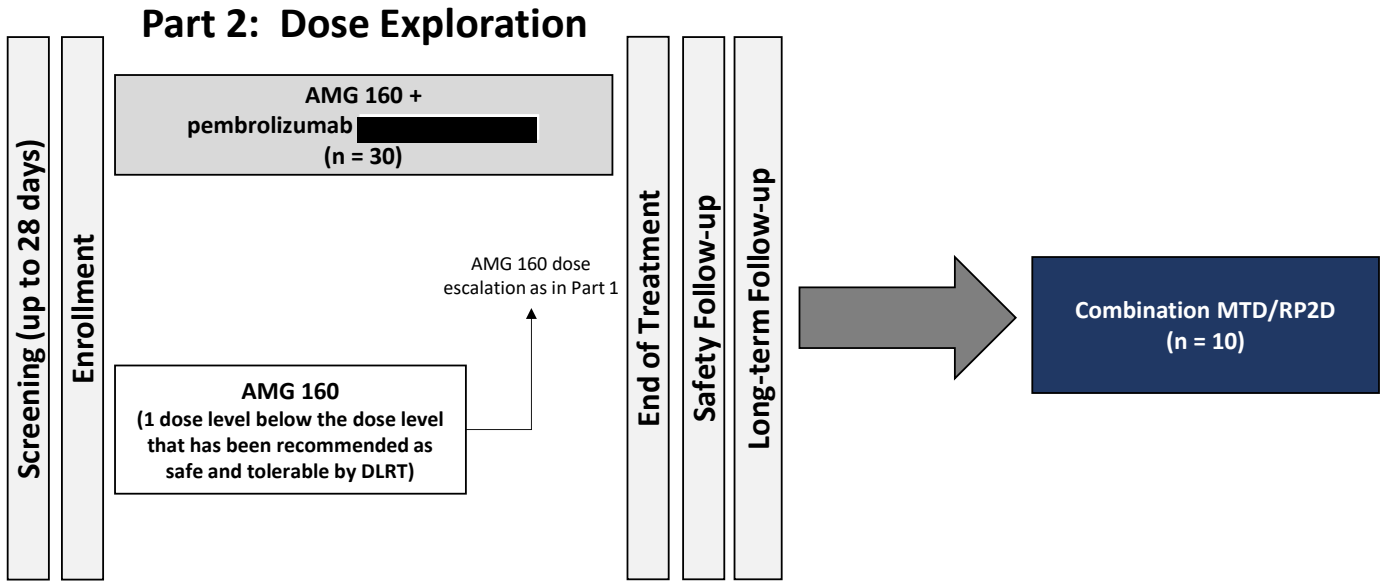


MTD = maximum tolerated dose; RP2D = recommended phase 2 dose

Study Periods:

- Screening: up to 28 days before enrollment
- Treatment: AMG 160 administered IV every 2 weeks (cycle 1 exception for extended IV infusion); treatment continues until progression (treatment beyond disease progression may be allowed as per PCWG3 guidelines)
- End of treatment: should occur as soon as possible (within 14 days) after the last dose of investigational product
- Safety follow-up: approximately 30 (+3) days after the end of the last dose of AMG 160, or prior to initiation of other therapy, whichever occurs first
- Long-term follow-up: every 6 months up to 3 years from the first dose of protocol-required therapy for all subjects who have not withdrawn consent

Figure 2. Part 2 Study Schema

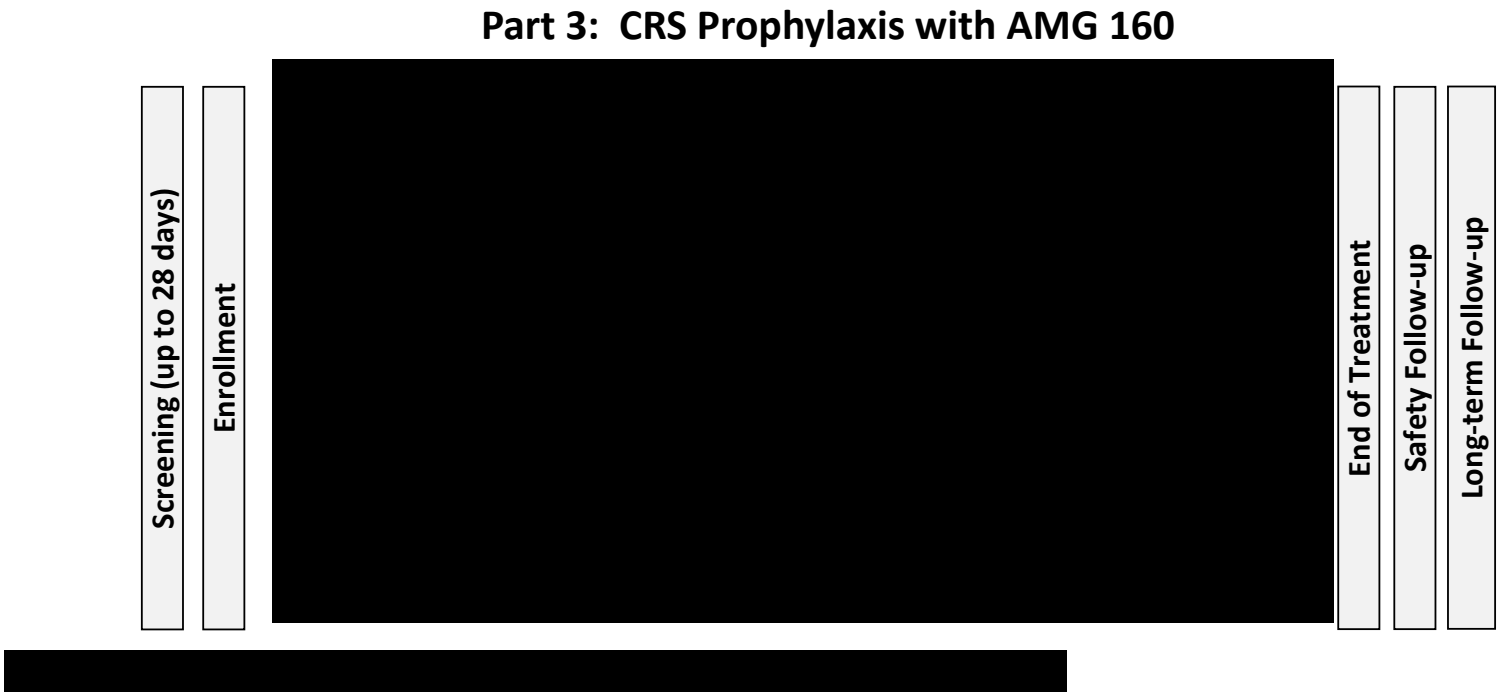


DLRT = Dose Level Review Team; [redacted]; MTD = maximum tolerated dose; [redacted] RP2D = recommended phase 2 dose

Study Periods:

- **Screening: up to 28 days before enrollment**
- **Treatment: AMG 160 administered IV every 2 weeks (except if step-dosing or extended IV infusion is implemented in cycle 1); pembrolizumab [redacted] treatment continues until progression (treatment beyond disease progression may be allowed as per PCWG3 guidelines)**
- **End of treatment: should occur as soon as possible (within 14 days) after the last dose of investigational product**
- **Safety follow-up: approximately 30 (+3) days after the end of the last dose of AMG 160, or prior to initiation of other therapy, whichever occurs first**
- **Long-term follow-up: every 6 months up to 3 years from the first dose of protocol-required therapy for all subjects who have not withdrawn consent**

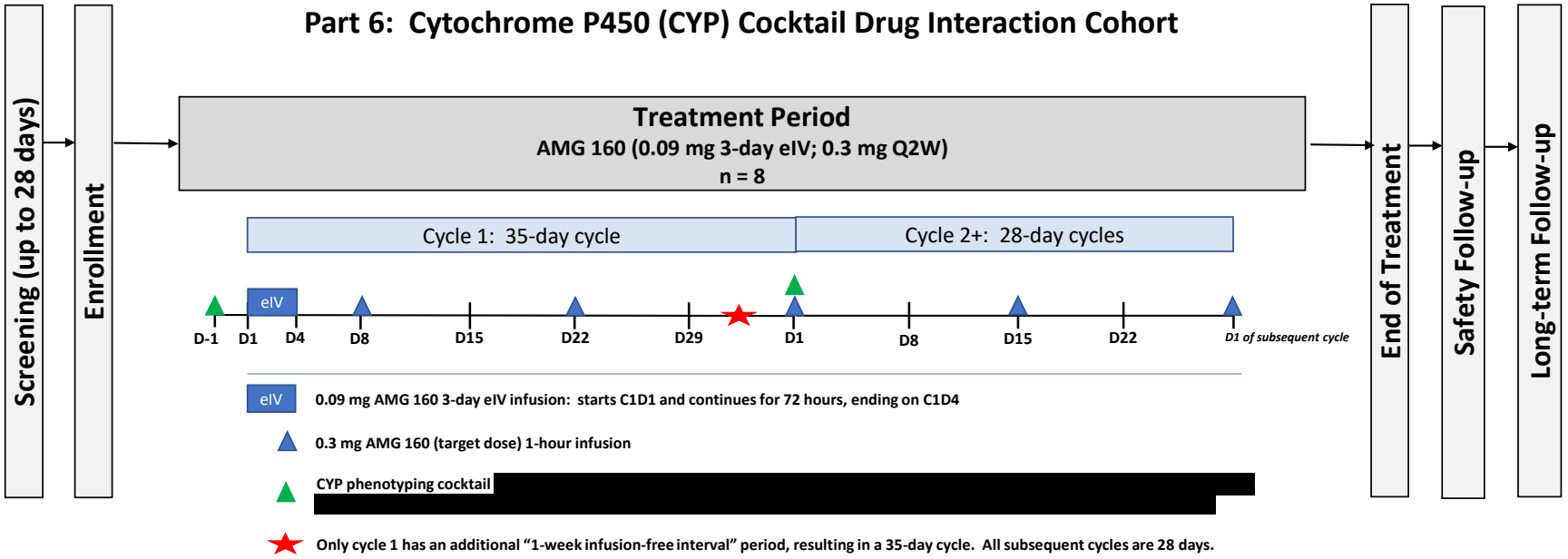
Figure 3. Part 3 Study Schema



Study Periods:

- **Screening: up to 28 days before enrollment**
- **Treatment: AMG 160 administered IV every 2 weeks (cycle 1 exception for step-dosing or extended IV infusion); treatment continues until progression (treatment beyond disease progression may be allowed as per PCWG3 guidelines)**
- **End of treatment: should occur as soon as possible (within 14 days) after the last dose of investigational product**
- **Safety follow-up: approximately 30 (+3) days after the end of the last dose of AMG 160, or prior to initiation of other therapy, whichever occurs first**
- **Long-term follow-up: every 6 months up to 3 years from the first dose of protocol-required therapy for all subjects who have not withdrawn consent**

Figure 4. Part 6 Study Schema



C1D1 = cycle 1 day 1; eIV = extended intravenous; PCWG3 = Prostate Cancer Working Group 3; Q2W = every 2 weeks

<u>Study Periods</u>:

- Screening: up to 28 days before enrollment
- Treatment: AMG 160 administered IV every 2 weeks (cycle 1 exception for extended IV infusion); treatment continues until progression (treatment beyond disease progression may be allowed as per PCWG3 guidelines). CYP phenotyping cocktail to be administered one day prior to cycle 1 day 1 (~24 hours prior to AMG 160 infusion) and on cycle 2 day 1 (immediately after AMG 160 infusion).
- End of treatment: should occur as soon as possible (within 14 days) after the last dose of investigational product
- Safety follow-up: approximately 30 (+3) days after the end of the last dose of AMG 160, or prior to initiation of other therapy, whichever occurs first
- Long-term follow-up: every 6 months up to 3 years from the first dose of protocol-required therapy for all subjects who have not withdrawn consent

3.2 Sample Size

It is anticipated that approximately 218-288 subjects will be enrolled in this study. See protocol Section 5.2 for detailed breakdown of sample size by part and cohort.

Part 1

The sample size in the dose-escalation phase is based on practical consideration and is consistent with conventional oncology studies with the objective to estimate the MTD. With 3-4 subjects in a cohort, there is a 27% to 70% probability of observing at least 1 DLT if the true DLT rate is 10% to 33% and with 6 subjects in a cohort, there is a 47% to 91% probability.

In the dose-expansion cohort, a subject number of 50 will provide a 92% probability of observing at least 1 adverse event with 5% incidence rate. An exact 95% binomial CI will be provided for overall response rate. With approximately 50 enrolled subjects, a two-sided 95% CI of objective response rate per RECIST 1.1 (PCWG3 modifications), ORR, will extend at most 23% in length from the observed ORR, ie, if the estimated ORR is 50%, the estimated 95% CI of ORR will be within (27%, 73%). This is assuming the true ORR is approximately 50% and the proportion of subjects with RECIST measurable disease is about 40%.

With 3 subjects at the initial safety review, there is a 27% to 70% probability of observing at least 1 DLT, if the true DLT rate is 10% to 33%. With 9 subjects, there is a 37% to 61% probability of observing a DLT, if the true DLT rate is 5% to 10%. Intensive pharmacokinetic sampling from combined 9 subjects will allow adequate characterization of AMG 160 pharmacokinetics in [redacted] subjects respectively.

Part 2

For Part 2 (AMG 160 Combination with Pembrolizumab), sample size (n = 30) is based on practical considerations consistent with oncology studies with the objective to determine the MTD based on DLTs. With the total subject number of 20 treated at a combination, it will provide a 79% probability of observing at least one DLT with 5% incidence rate and 96% probability of observing at least one DLT with 10% incidence rate.

Part 3

For Part 3 (etanercept prophylaxis for AMG 160-related CRS), sample size (n = 20) is based on practical considerations consistent with oncology studies to determine

administering AMG 160 with etanercept prophylaxis only. With the total subject number of 20 treated at a combination, it will provide a 64% probability of observing at least 1 DLT with 5% incidence rate and 88% probability of observing at least 1 DLT with 10% incidence rate.



Part 6

For Part 6 (Cytochrome P450 [CYP] Cocktail Drug Interaction Cohort), sample size (up to 8) is based on practical considerations consistent with oncology studies. With the total subject number of 8 subjects treated at a combination, it will provide a 36% probability of observing at least 1 DLT with 5% incidence rate and 57% probability of observing at least 1 DLT with 10% incidence rate.

3.3 Adaptive Design

For Part 1 (AMG 160 Monotherapy), a 2-parameter BLRM (Neuenschwander et al, 2008) is used to guide dose exploration. The design seeks to identify the MTD or RP2D, which is defined as a dose most likely to have a DLT rate in the target toxicity probability interval (TPI), but with overdose control that limits the possibility the dose has an excessive or unacceptable DLT rate (Babb et al, 1998). In this study, the target TPI is defined as (0.20, 0.33] and excessive and unacceptable TPIs are defined as (0.33, 0.60] and (0.60, 1.00], respectively, with an overdose control limit of less than 0.40 probability

of excessive or unacceptable TPI. The probability of a DLT at dose level di is assumed to follow a Bernoulli distribution with probability pi where the logit of pi increases linearly with the log of the standardized dose in the following 2-parameter logistic model:

$$\log [pi / (1-pi)] = \text{logit}(pi) = \log[a] + \exp(\log[b]) \log (di / dref)$$

where a and b are random variables and dref is one of the planned dose selected as the reference dose.

A bi-variate normal prior distribution was selected for theta = (log a, log b). The mean/standard deviation for "log a" were selected as -1.099/1.122 and for "log b" as -1.243/1.981 with a correlation of 0. These values were selected such that pi is 0.05 for the initial planned dose (0.003 mg) and 0.25 for the reference dose ([redacted] mg), where the probability that the true DLT rate is $\leq$ 0.40 at the lowest dose is 0.90 and the probability the true DLT rate is $\leq$ 0.05 at the reference dose is 0.05.

Operating characteristics of this design are described in protocol Section 12.8.

The dose expansion stopping rules described in protocol Section 7.4.1.2 are derived using a Bayesian approach developed in 1995 by Thall et al, 1995. The prior distribution describing the event rate is a Beta (0.40, 1.60) distribution. The threshold for terminating the study is a posterior probability $>$ 80% for an event rate greater than 20%.

In Part 2 (AMG 160 Combination with Pembrolizumab), dose escalation decisions will be guided by the modified toxicity probability interval design (mTPI-2). See Appendix D for additional information.

4. Covariates and [redacted]

4.1 Planned Covariates

Not applicable

[redacted]

5. Definitions

5.1 Study Endpoints

5.1.1 Primary Endpoints Definitions

Dose-limiting Toxicities (DLTs)

Investigators determine whether a TEAE qualifies as a DLT per the definition described in protocol Section 7.4.1.3. For an adverse event to qualify as a DLT, the start date must be within 28 days from the date of the first dose of investigational product (AMG 160 or Pembrolizumab).

Treatment-Emergent Adverse Event (TEAE)

A treatment-emergent AE occurs on or after the first dose of AMG 160 or Pembrolizumab as determined by the flag indicating if the AE started prior to the first dose on the AE eCRF and up to 30 days after the last dose of AMG 160 or Pembrolizumab**, whichever is later,** excluding events reported after End of Study date or start of new anti-cancer therapy whichever occurs first.

Treatment-Related Adverse Event (TRAE)

A TRAE is any treatment-emergent AE that is not clearly attributable to causes other than AMG 160 treatment. Event with missing relationship will be assumed to be treatment-related.

Fridericia-corrected QT Interval (QTcF) :

The Fridericia correction will be calculated from the QT (msec) and RR interval (msec), as follows:

$QTcF=QT/(RR/1000)^{0.33}$

where RR (msec) = 60 x 1000 / HR

5.1.2 Secondary Endpoints Definitions

Objective Response (OR) per RECIST 1.1

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 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. Derivation details is in Appendix C**.**

CTC0 Response

CTC0 response is defined as CTC0 (reduction of CTCs > 0 to 0) at any post-baseline measurement. CTC0 response is applicable only for subjects with baseline CTC > 0.

CTC conversion

CTC conversion is defined as ≥5 CTCs/7.5 mL blood to ≤ 4 CTCs/7.5 mL blood at any post-baseline measurement. CTC conversion is applicable only for subjects with baseline CTC ≥ 5.

PSA Response (PSA 30):

A PSA response (PSA 30) is defined as a ≥ 30% reduction from the baseline PSA. This PSA response must be confirmed by a second consecutive value ≥ 3 weeks later. This applies only to subjects with measurable (i.e., > 0) baseline PSA.

PSA Response (PSA 50):

A PSA response (PSA 50) is defined as a ≥ 50% reduction from the baseline PSA. This PSA response must be confirmed by a second consecutive value ≥ 3 weeks later. This applies only to subjects with measurable (i.e., > 0) baseline PSA.

PSA Response (PSA 70):

A PSA response (PSA 70) is defined as a ≥ 70% reduction from the baseline PSA. This PSA response must be confirmed by a second consecutive value ≥ 3 weeks later. This applies only to subjects with measurable (i.e., > 0) baseline PSA.

PSA Response (PSA 90):

A PSA response (PSA 90) is defined as a ≥ 90% reduction from the baseline PSA. This PSA response must be confirmed by a second consecutive value ≥ 3 weeks later. This applies only to subjects with measurable (i.e., > 0) baseline PSA.

Overall survival (OS)

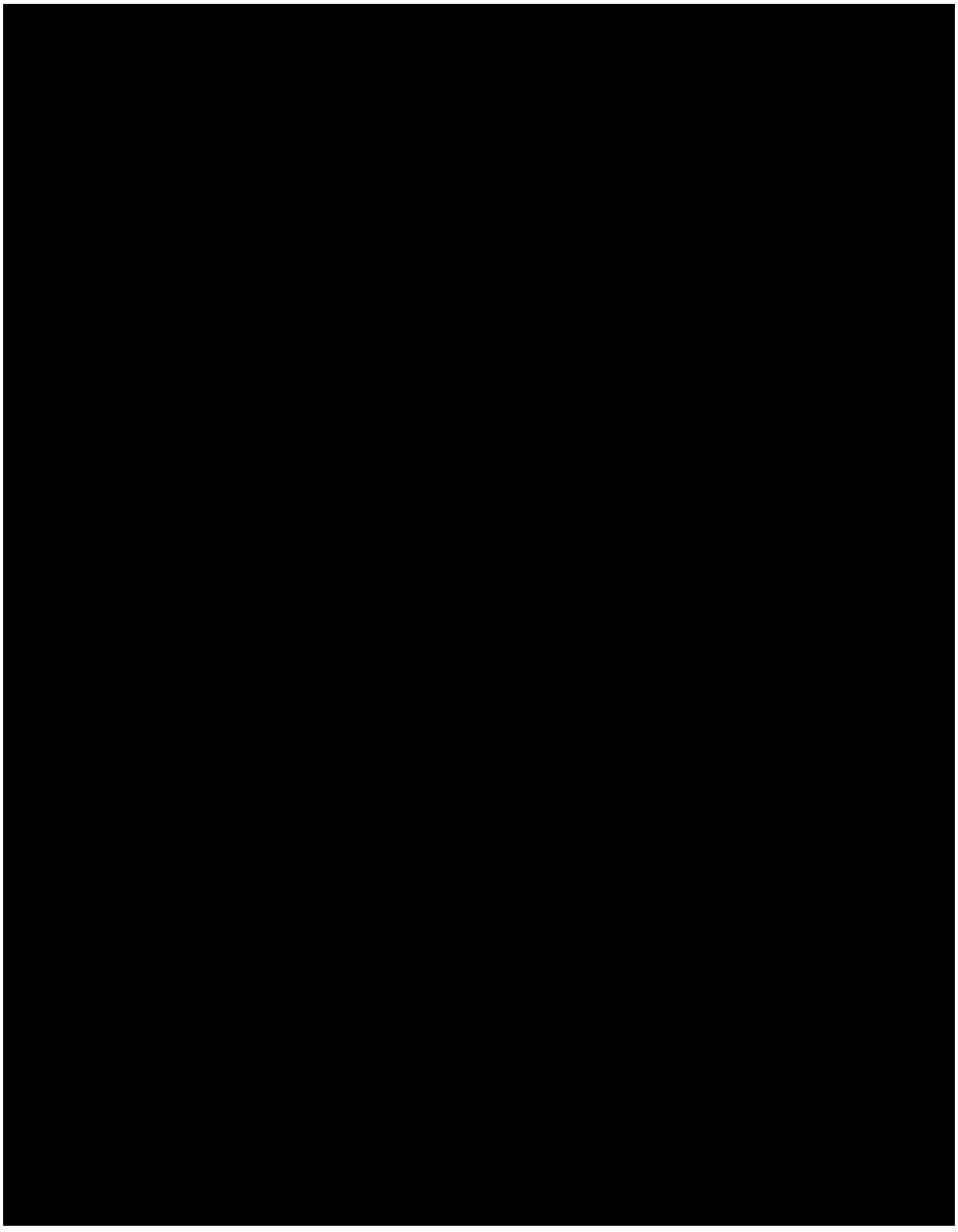
Overall survival is defined as the time from the date of Study Day 1 until death due to any cause:

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.

Last known alive date

For subjects who have complete death date available on End of Study and Long-term Follow-up/Survival Status (Oncology) form, the last known alive date will be Death Date minus 1.





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 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. Additional censoring rules are as follows:

Censoring rules for Duration of Response (DOR):

- 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.

Data for responders who have the last evaluable scan followed > X days later by disease progression or death are censored at the time of last evaluable tumor

assessments by CT/MRI scan. More details about the censoring rules are included in Appendix F.

Duration of PSA Response (PSA DOR)

PSA DOR is defined as the time from the date of an initial PSA response (PSA 50) 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. This endpoint only applies to subjects with a PSA response (PSA 50).

More details about the censoring rules are included in Appendix F.

Radiographic Progression:

A radiographic progression occurs if either of the following occurs:

Progressive disease per RECIST 1.1 occurs.

Bone disease progression 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 the first post-treatment bone scan (e.g., week 8). 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 a second scan showing persistence of the additional lesions relative to the first post-treatment scan (e.g., week 8).

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 criteria in Appendix F.

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 until 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.

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 no post-baseline PSA measurement and a vital status of alive or unknown, PSA PFS will be censored at Study Day 1.

More details about the censoring rules are included in Appendix F.

Time to Radiographic Progression

Time to radiographic progression is defined as the time from Study Day 1 until the first documentation of radiographic disease progression in the absence of subsequent anticancer therapy. Time to radiographic progression will be censored at the last evaluable post-baseline tumor assessment prior to subsequent anti-cancer therapy; otherwise, at Study Day 1.

More details about the censoring rules are included in Appendix F.

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 on the date of the last PSA measurement. If a subject has no baseline or no post-baseline PSA measurement, time to PSA progression will be censored at Study Day 1.

More details about the censoring rules are included in Appendix F.

Gallium PSMA-11 Response

A Gallium PSMA-11 response is a ≥50% reduction from baseline in the maximum SUV using 68Gallium (^{68}Ga)-prostate-specific membrane antigen (PSMA)-11 positron emission tomography (PET)/computed tomography (CT).

FDG PET Response

A FDG PET response is a ≥50% reduction from baseline in the maximum SUV using ^{18}F-fluorodeoxyglucose (FDG) PET/CT.

Symptomatic Skeletal Events (SSE)

A SSE is defined per PCWG3 as any of the following which is collected on the events eCRF:

- 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

Time to SSE

Time to SSE is defined as time from Study Day1 to the first SSE. Otherwise, SSE is censored at the last dose date of AMG 160 or Pembrolizumab or end of safety follow up date, whichever is later.

Neutrophil-to-lymphocyte ratio (NLR):

NLR is calculated by dividing the number of absolute neutrophils by the number of lymphocytes.

C_{max}

Maximum observed AMG 160 serum concentration during the dosing interval.

Half-life ($t_{1/2}$)

Time required for AMG 160 serum concentration to reduce to half the maximum concentration value (C_{max})

T_{max}

Time of maximum observed AMG 160 serum concentration during the dosing interval.

Evaluable tumor assessment

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. A visit overall response other than not evaluable (NE) for RECIST 1.1.

5.1.3 Exploratory Endpoints Definitions

[redacted]

5.2 Study Time Points

Enrollment Date:

A subject is considered as enrolled when the investigator decides that the subject has met all eligibility criteria. The investigator should document this decision and date in the subject's medical record and in the enrollment case report form.

Study Day 1:

Defined as the date of the first dose of the investigational product (AMG 160 or Pembrolizumab) is administered to the subject.

End of Study for Individual Subject:

End of study for individual subject is defined as the date of the final study visit assessments and/or procedures are performed.

End of Study (Primary Completion):

End of study primary completion is 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).

End of Study:

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.

End of Treatment:

End of treatment is defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject. End of treatment: should occur as soon as possible (within 14 days) after the last dose of investigational product (AMG 160 or Pembrolizumab).

Safety follow-up Visit:

Upon permanent discontinuation from the study treatment for any reason, a safety follow-up visit will be performed approximately 30 (+ 3) days after the end of the last dose of AMG 160 or prior to initiation of other therapy, whichever occurs first.

Long-term follow-up Visit:

Long-term follow-up visit will be conducted every 6 months up to 3 years from the first dose of AMG 160 or Pembrolizumab for all subjects who have not withdrawn consent by

clinic visit, telephone or chart review to assess for survival and/or the commencement of subsequent cancer therapy.

5.3 Demographics and Baseline Related Definitions

Age at enrollment:

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

Baseline:

The baseline is defined as the last non-missing value on or prior to the **first** dose of AMG 160 or Pembrolizumab , **whichever occurs first**.

Baseline for Triplicates ECG:

Baseline for ECG is defined as mean of the 3 triplicate ECG results. If fewer than 3 triplicate ECG results are available, the mean of available triplicate should be calculated. For all post baseline ECG, the mean of one triplicate ECG results at the same assessment will be calculated and used in the analysis.

When an ECG is missing within a triplicate, all available data will be averaged for that timepoint.

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]x100

Body Mass Index (BMI)

Body Mass Index should be calculated using the following formula

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

6. Analysis Sets

6.1 Safety Analysis Set

The analysis of all endpoints, unless noted otherwise, will be conducted on the Safety Analysis Set defined as all subjects that are enrolled and receive at least 1 dose of AMG 160 or Pembrolizumab.

6.2 Pharmacokinetic/Pharmacodynamic Analyses Set(s)

Pharmacokinetic (PK) Concentration Analysis Set: The PK Concentration Analysis Set will include all subjects who received investigational product (AMG 160 or Pembrolizumab) and have at least 1 PK concentration available for analysis. 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 that are enrolled, receive at least 1 dose of AMG 160 or Pembrolizumab, have measurable baseline disease per RECIST 1.1 with PCWG3 modifications per protocol and had the opportunity to be followed for at least 9 weeks starting from Study Day 1. Subjects who stopped disease assessment prior to 9 weeks will be included in this analysis set if the data cutoff is at least 9 weeks after their first study dose date.

6.3.2 PSA Response Evaluable Analysis Set

PSA Response Evaluable Analysis Set is defined as all subjects that are enrolled, receive at least 1 dose of AMG 160 or Pembrolizumab, have a measurable (i.e., > 0) baseline PSA and had the opportunity to be followed for at least 9 weeks starting from Study Day 1. Subjects who stopped disease assessment prior to 9 weeks will be included in this analysis set if the data cutoff is at least 9 weeks after their first study dose date.

6.3.3 CTC Evaluable Analysis Set

CTC Evaluable Analysis Set is defined as all subjects that are enrolled, receive at least 1 dose of AMG 160 or Pembrolizumab and have baseline CTC >0.

6.3.4 CTC Conversion Analysis Set

CTC Conversion Analysis Set is defined as all subjects that are enrolled, receive at least 1 dose of AMG 160 or Pembrolizumab and have baseline CTC ≥5.

6.3.5 DLT Evaluable Analysis Set

The analysis of DLT will be conducted on the DLT Analysis Set defined as all subjects from the Safety Analysis Set that are DLT evaluable per protocol Section 10.2.1.

7. Planned Analyses

7.1 Interim Analysis and Early Stopping Guidelines

Safety data will be reviewed on an ongoing basis. For Part 1 (AMG 160 Monotherapy), based on accumulating toxicity information, BLRM will be used to make dosing recommendations. The DLRT will formally review safety data in dose level review meetings (DLRMs). 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 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.

The futility analysis of PSA30 will be performed when the first 30 evaluable subjects reach cycle 3 day 1 for subjects in Part 1 dose expansion. If the posterior probability of PSA30 response < 18% is > 70% for the first 30 evaluable subjects, the cohort will be declared futile. Equivalently, if < 5 PSA30 responders are observed in a cohort, the cohort will be declared futile. The posterior probability is calculated based on a noninformative prior distribution Beta (0.5, 0.5). The probability of stopping at futility if PSA30 ≤ 18% is approximately 35% (see Figure 10-1 in Study Protocol).

In Part 2 (AMG 160 Combination with Pembrolizumab), dosing recommendations will be guided by the modified toxicity probability interval design (mTPI-2). See Protocol Section 12.16 in Study Protocol for additional information.

A formal interim analysis of available safety and efficacy data will occur when all remaining dose-escalation subjects have had the opportunity to complete 28 days on study for Part 1. A similar interim analysis will be conducted for Part 2 when all remaining subjects have had the opportunity to complete 28 days on the study. This interim analysis will estimate the MTD (MTD1, MTD2, MTD3, and/or MTD4, as

applicable if step-dosing is implemented), support the determination of the RP2D, and support the evaluation of benefit/risk profile of AMG 160 as monotherapy and in combination with Pembrolizumab.

[redacted]

An interim analysis will not be performed for Part 3 and Part 6 (will be part of the final analysis).

In interim analysis for Part 2 and [redacted] the data will be analyzed **based on the 'as is' data snapshot** .

[redacted]

[redacted]

7.2 Primary Analysis

The primary analysis will only include Part 1 dose exploration (excluding [redacted]) and Part 1 dose-expansion cohort 1a. Other parts will be analyzed as part of the final 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. The data will be analyzed once they have been entered, cleaned and locked.

7.3 Final Analysis

The final analysis will occur when target enrollment is complete for all 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. The data will be analyzed once they have been 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

[redacted]

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 will not be imputed.

All subjects with a post-baseline assessment will have a baseline assessment. Therefore, the analysis model must impute baseline and post-baseline records for subjects who have at least one post baseline assessment with a value of 'NO RESULT' for the value of the antibody measure at baseline.

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

Values below the quantification limits will be set to zero for these secondary endpoint labs: alkaline phosphate [total, bone], LDH, hemoglobin, neutrophil-to-lymphocyte ratio, urine N-telopeptide.

Imputation Rules for Partial or Missing Start Dates:

Missing or incomplete dates will be listed as it is in any listings.

[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 decisions 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 all 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 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 [redacted] data by treatment (monotherapy vs combination with pembrolizumab), 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

A summary of subject disposition and investigational product (AMG 160 or Pembrolizumab) disposition will be provided for all subjects enrolled in the study. A subject disposition listing, noting inclusion in each analysis subset, will be provided for all subjects enrolled. A subject listing noting duration of investigational product (AMG 160 or Pembrolizumab) administration, reason for discontinuation of treatment, and reason for discontinuing study will be provided. A list of subjects screened but not enrolled (screen failures) will be provided.

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.

9.4 Demographic and Baseline Characteristics

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

- Age (years) at enrollment (continuous summary statistics)
- Sex (number and percentage of males and females)
- Ethnicity (number and percentage in each ethnicity category)
- Race (number and percentage of subjects in each race, or mixed-race combination)
- Eastern Cooperative Oncology Group (ECOG) Performance Status

9.5 Efficacy Analyses

Table 1. Secondary Efficacy Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method	Analysis Set
Objective response (OR) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1	The proportion of subjects with an objective response per RECIST 1.1 along with corresponding exact 95% CI will be calculated using the Clopper-Pearson method (Clopper and Pearson, 1934). Waterfall plots for the maximum percent decrease from baseline in sums of longest diameters will also be provided.	RECIST 1.1 Evaluable Analysis Set Applicable for all subjects with baseline measurable disease and post-baseline evaluable tumor response assessment.
Prostate-specific antigen (PSA) response (30%, 50%, 70%, 90%)	The proportion of subjects with PSA response (30%, 50%, 70%, 90%) and 95% CI calculated by Clopper-Pearson Method (Clopper and Pearson, 1934) will be reported for PSA response. Waterfall plot for the maximum percent decrease from baseline PSA will be presented.	PSA Response Evaluable Analysis Set Applicable to all subjects with a measurable (ie, > 0) baseline PSA and post-baseline PSA assessment
Prostate-specific antigen (PSA)	The sensitivity analysis will be done for PSA response evaluable subjects with at least	Applicable to all subjects with a measurable (ie. >0) baseline PSA and at least

Endpoint	Primary Summary and Analysis Method	Analysis Set
response sensitivity analysis	two post-baseline PSA measurements. The proportion of subjects with PSA response and 95% CI calculated by Clopper-Pearson Method (Clopper and Pearson, 1934) will be reported for PSA response.	two post-baseline PSA measurements
Duration of response (DOR) (per RECIST 1.1)	Descriptive statistics will be presented. The median and other percentiles, as appropriate, will be presented using the Kaplan-Meier curve. The corresponding 95% confidence intervals for the median and quartiles will be constructed using the method of Klein and Moeschberger (1997) with log-log transformation. The duration of the follow-up will be estimated by reverse Kaplan-Meier method (Schemper and Smith 1996). This endpoint only applies to subjects with an objective response.	RECIST 1.1 Evaluable Analysis Set – Objective Responders
Duration of response (DOR) (PSA).	Descriptive statistics will be presented. The median and other percentiles, as appropriate, will be presented using the Kaplan-Meier curve.	PSA Response Evaluable Analysis Set – PSA50 responders

Endpoint	Primary Summary and Analysis Method	Analysis Set
	The corresponding 95% confidence intervals for the median and quartiles will be constructed using the method of Klein and Moeschberger (1997) with log-log transformation. The duration of the follow-up will be estimated by reverse Kaplan-Meier method (Schemper and Smith 1996). This endpoint only applies to subjects with a PSA50 response.	
68Gallium (68Ga)-prostate-specific membrane antigen (PSMA)-11 positron emission tomography (PET)/computed tomography (CT) and 18F-fluorodeoxyglucose (FDG) PET/CT based response evaluation (Parts [redacted] and 6 are not included)	The proportion of subjects and 95% CI calculated by Clopper-Pearson Method (Clopper and Pearson, 1934) will be reported.	Safety Analysis Set
Time to Progression (TTP) (radiographic).	The median and other percentiles, as appropriate, will be presented using the Kaplan-Meier curve. The corresponding 95% confidence intervals for the	Safety Analysis Set

Endpoint	Primary Summary and Analysis Method	Analysis Set
	median and quartiles will be constructed using the method of Klein and Moeschberger (1997) with log-log transformation. The duration of the follow-up will be estimated by reverse Kaplan-Meier method (Schemper and Smith 1996).	
Time to Progression (TTP) (PSA).	The median and other percentiles, as appropriate, will be presented using the Kaplan-Meier curve. The corresponding 95% confidence intervals for the median and quartiles will be constructed using the method of Klein and Moeschberger (1997) with log-log transformation. The duration of the follow-up will be estimated by reverse Kaplan-Meier method (Schemper and Smith 1996).	Safety Analysis Set
Radiographic Progression Free Survival (rPFS)	The median and other percentiles, as appropriate, will be presented using the Kaplan-Meier curve. The corresponding 95% confidence intervals for the median and quartiles will be constructed using the method of Klein and Moeschberger (1997) with log-log transformation. The	Safety Analysis Set

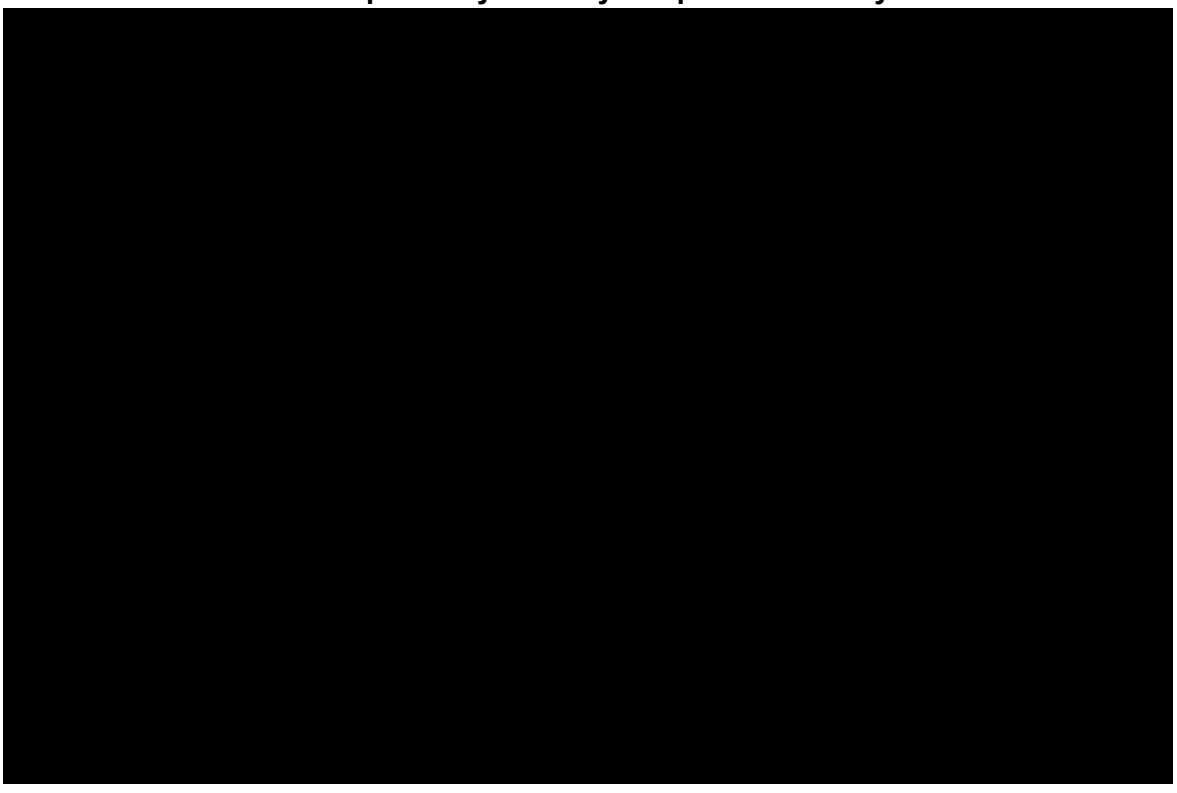
Endpoint	Primary Summary and Analysis Method	Analysis Set
	duration of the follow-up will be estimated by reverse Kaplan-Meier method (Schemper and Smith 1996).	
PSA Progression Free Survival (PSA PFS)	The median and other percentiles, as appropriate, will be presented using the Kaplan-Meier curve. The corresponding 95% confidence intervals for the median and quartiles will be constructed using the method of Klein and Moeschberger (1997) with log-log transformation. The median and quartiles for the duration of the follow-up will be estimated by reverse Kaplan-Meier method (Schemper and Smith 1996).	Safety Analysis Set
1, 2, and 3-year overall survival (OS).	The median and other percentiles, as appropriate, will be presented using the Kaplan-Meier curve. The corresponding 95% confidence intervals for the median and quartiles will be constructed using the method of Klein and Moeschberger (1997) with log-log transformation. The median and quartiles for the duration of the follow-up will be estimated by reverse Kaplan-	Safety Analysis Set

Endpoint	Primary Summary and Analysis Method	Analysis Set
	Meier method (Schemper and Smith 1996).	
Circulating tumor cells (CTCs) – CTC0 response	The proportion of subjects with CTC0 response with 95% CI calculated by Clopper-Pearson Method (Clopper and Pearson, 1934) will be reported.	CTC Evaluable Analysis Set
Rate of CTC conversion	The proportion of subjects with Circulating tumor cells Conversion with 95% CI calculated by Clopper-Pearson Method (Clopper and Pearson, 1934) will be reported.	CTC Conversion Analysis Set
Time to symptomatic skeletal events	Descriptive statistics will be presented. The median and other percentiles, as appropriate, will be presented using the Kaplan-Meier curve. The corresponding 95% confidence intervals for the median and quartiles will be constructed using the method of Klein and Moeschberger (1997) with log-log transformation. The duration of the follow-up will be estimated by reverse Kaplan-Meier method (Schemper and Smith 1996).	Safety Analysis Set

Endpoint	Primary Summary and Analysis Method	Analysis Set
Alkaline phosphatase [total, bone], lactate dehydrogenase [LDH], hemoglobin, neutrophil-to-lymphocyte ratio, urine N-telopeptide)	Summary statistics by time point will be provided. Waterfall plots for the maximum percent improvement from baseline will be presented.	Safety Analysis Set

Analysis of objective response (including ORR, DOR) and radiographic progression (including rPFS, TTP) will be based on independent radiological assessment and by investigator separately. Analysis of concordance in tumor response and disease progression by independent radiographical assessment and by investigator will be performed.

Table 2. Exploratory Efficacy Endpoint Summary Table





9.6 Safety Analyses

9.6.1 Analyses of Primary Safety Endpoint(s)

Table 3. Safety Endpoint Summary Table

Endpoint	Statistical Analysis	Analysis Set
Dose Limiting Toxicities (DLTs)	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 Bayesian Logistics Regression Model. If one or more subjects experience late onset adverse events as defined in Section 9.6.2 of the statistical analysis plan, a sensitivity analysis will be done. The probability of a subject having either a DLT or late onset adverse events by dose level will be estimated	DLT Evaluable Analysis Set

	using a two-parameter Bayesian Logistics Regression Model.	

9.6.2 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 or later will be used to code all events categorized as adverse events and disease-related 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 and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product (AMG 160 or Pembrolizumab) or other protocol-required therapies, and significant treatment-emergent adverse events will also be provided. Subject incidence of disease-related events, serious disease-related events, and fatal disease-related events, will be tabulated by system organ class and preferred term.

Disease-related events are events anticipated to occur in the study population due to the underlying disease. Refer to protocol Section 12.11 for the list of disease-related events.

Disease-related events that would qualify as an adverse event or serious adverse event: An event based on the underlying disease that is worse than expected as assessed by the investigator for the subject's condition or if the investigator believes there is a causal relationship between the investigational product(s) (AMG 160 or Pembrolizumab)/study treatment/protocol-required therapies and disease worsening, this must be reported as an adverse event or serious adverse event.

Disease-related events that do not qualify as adverse events or serious adverse events: An event which is part of the normal course of disease under study (e.g., disease progression in oncology or hospitalization due to disease progression) is to be reported as a disease-related event.

Late Onset Adverse Event

Late onset adverse event refers to any treatment-related adverse event that begins after the DLT period (more than 28 days after the date of the first dose of investigational product, i.e., AMG 160 or Pembrolizumab, which meets the following criteria.

- grade 4 or 5 toxicity

- grade 3 nausea, vomiting, or diarrhea that do not improve to grade ≤ 1 within 72 hours
- grade ≥ 3 neurologic events (headache, mental status changes, dysphasia, tremors, dysmetria, gait abnormalities, seizure) that do not improve to grade ≤ 1 within 7 days
- grade 3 adverse event lasting more than 3 days

The following adverse events will NOT be adjudicated as late onset adverse event regardless of the grade or duration:

- grade 3 fever
- grade 3 fatigue

9.6.3 Laboratory Test Results

Individual chemistry, hematology and urinalysis laboratory data will be listed, 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 will include summary statistics over time and/or changes from baseline over time may be provided. 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 will include summary statistics over time and/or changes from baseline over time may be provided. 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 assessed 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. Subjects' maximum post baseline values will also be categorized and the number and percentage of subjects in each group will be summarized. All on-study ECG data will be listed and select parameters of interest plotted.

The average of 3 triplicates will be used for the statistical analysis.

The Fridericia correction will be calculated from the QT (msec) and RR interval (msec), as

QTcF = QT/ (RR/1000)^0.33

If RR is missing and the respective record of HR is non-missing then conversion from HR to RR is

Instantaneous HR in cycle/min = 60/RR (in sec) OR

Instantaneous HR in cycle/min = 60000/RR (in msec)

[redacted]

9.6.8 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to investigational product (AMG 160 or Pembrolizumab) by planned dose level.

Descriptive statistics of total dose (mg), duration of usage, number and percentage of subjects with dose modifications, reasons for modification will be described.

9.6.9 Exposure to Other Protocol-required Therapy

All other protocol-required therapies, including glucocorticoids and tocilizumab/siltuximab, that are commercially available are not provided by Amgen (except if required by local regulation).

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

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

9.7 Other Analyses

9.7.1 Analyses of Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Endpoints

Serum concentrations of AMG 160 will be determined using a validated assay. PK parameters will include but are not limited to maximum observed concentration (C_{max}), minimum observed concentration (C_{min}) and area under the concentration-time curve

over the dosing interval [AUC] and if feasible half-life ($t_{1/2}$). Pharmacokinetic parameters will be estimated using standard non-compartmental approaches based on the PK analysis set and summarized by dose level using descriptive statistics but not limited to means, standard deviations, medians, minimums, and maximums.

Serum concentrations below the lower limit of quantifications will be set to zero for the estimation of the pharmacokinetic parameters for each subject and for the calculation of the summary statistic for each time point. Actual dosing and sampling time will be used for all calculations. The reasons for excluding any sample from the analyses will be provided.

Individual concentration-time data will be summarized by dose level. Individual concentration-time data will also be tabulated and presented graphically. Summary statistics will be computed for each sampling time and parameter as appropriate.

Additional PK analyses, including but not limited to analysis of the relationship between AMG 160 dose and exposure parameters (AUC and C_{max}) and dose proportionality assessments, may also be conducted. As appropriate, additional details of PK analyses will be described in a separate PK analysis plan.

[redacted]

10. Changes From Protocol-specified Analyses

Baseline definition updated by replacing 'Cycle 1 Day 1' with 'first dose' as the definition is now generalized to first non-zero dose of either AMG 160 or Pembrolizumab.

11. Literature Citations / References

American Cancer Society: Cancer Facts & Figures 2018. Atlanta, Georgia: American CancerSociety 2018. Available at https://www.cancer.org/content/dam/cancer-org/research/cancerfacts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf. Accessed 20 March 2018.

AMG 160 Investigator's Brochure. Thousand Oaks, CA. Amgen Inc.

Babb J, Rogatko A, Zacks S. Cancer Phase I Clinical Trias: Efficient Dose Escalation with Overdose Control. *Statistics in Medicine*. 1998;17:1103-1120.

Brookmeyer R, Crowley J. A confidence interval for the median survival time. *Biometrics*. 1982;38:29-41.

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

Enbrel (etanercept) [package insert]. Thousand Oaks CA: Amgen, Inc; September 2017.

Klein, J. P. and Moeschberger, M. L. (1997), Survival Analysis: Techniques for Censored and Truncated Data, New York: Springer-Verlag.Longo D, Duffey P, DeVita V, Wesley M, Hubbard S, Young R. The calculation of actual or received dose intensity: A comparison of published methods. Journal of Clinical Oncology 9:2042–2051, 1991.

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;34:1402-1418.

Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time.

Controlled Clinical Trials 17:343–346, 1996

Thall, P F, Simon RM, Estey EH. Bayesian sequential monitoring designs for single-arm trials with multiple outcomes. *Stat Med*. 1995;14:357–379.

New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *EUROPEAN JOURNAL OF CANCER* 45 (2009)228–247.

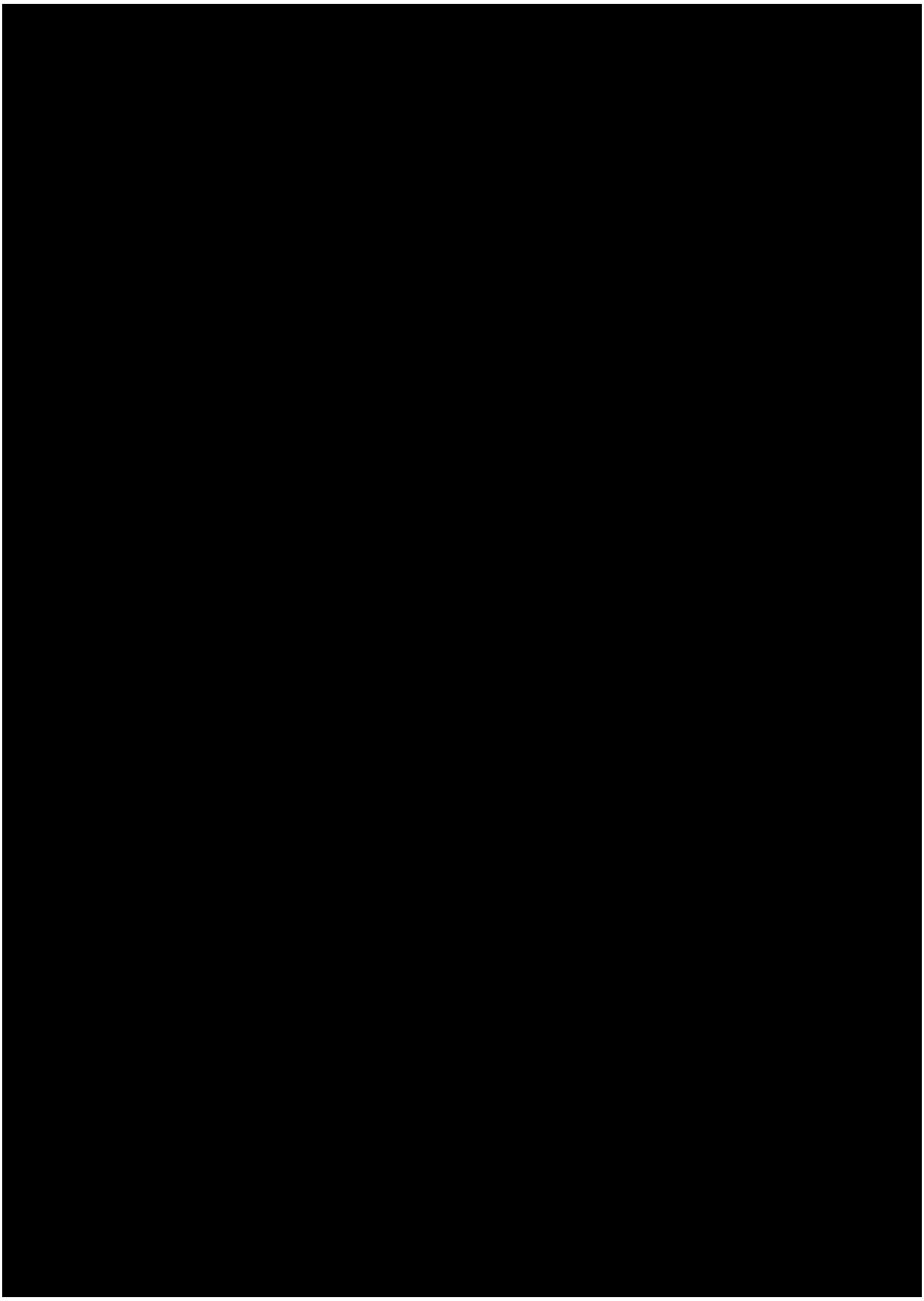
12. Prioritization of Analyses

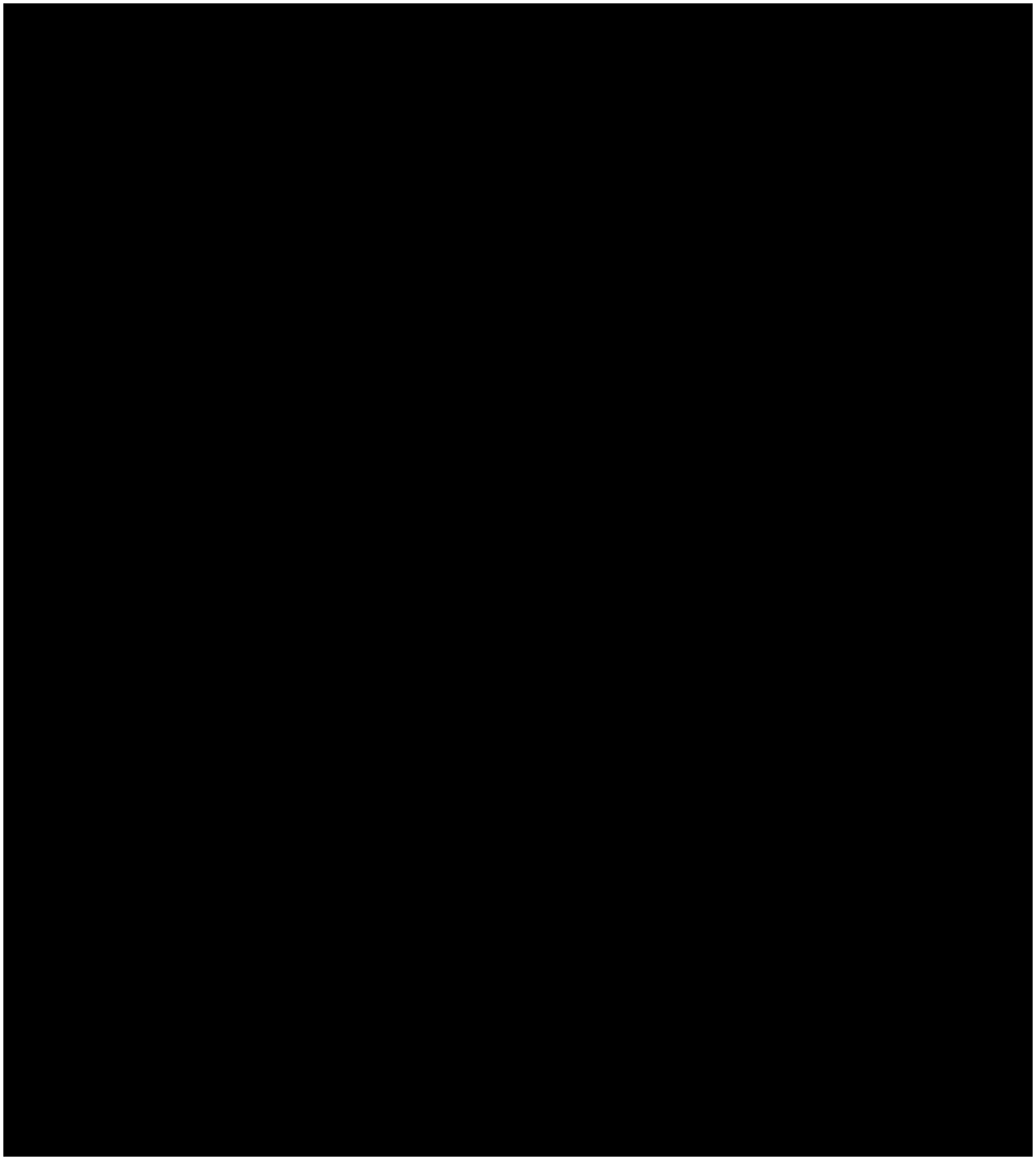
There is no prioritization of analyses.

13. Data Not Covered by This Plan

[redacted]

14. Appendices





Appendix B. Code Fragments

95% Confidence Interval by Clopper Pearson Method:

proc freq data=<data> ;

tables <variable>*<variable> / binomial(exact) ;

run;

Kaplan Meier Method:

proc lifetest data=<data>;

time T * Status(0);

run;

where T is time to event, Status is censoring variable and 0 is flagged for censored observation

Appendix C. 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.



Table 4. Confirmed BOR per RECIST 1.1 where Confirmation of CR/PR is Required

Criterion	Timepoint T1 Response	T1 ≥ 49 days after Baseline?	Timepoint T2 Response	T2 ≥ 49 days after Baseline?	T2 ≥ 28 days after T1?	BOR
C1	CR	Yes	CR	-	Yes	CR
C2			CR	-	No	SD
C3			PR, SD	-	-	Query data*
C4			PD	-	-	SD
C5			NE, No further evaluations			SD
C6		No	CR	-	Yes	CR
C7			CR	Yes	No	SD
C8			PR, SD	-	-	Query data*
C9			PD	-	-	PD
C10			NE, No further evaluations			NE
C11	PR	Yes	CR, PR	-	Yes	PR
C12			CR, PR	-	No	SD
C13			SD	-	-	SD
C14			PD	-	-	SD
C15			NE, No further evaluations			SD

C16		No	CR, PR	-	Yes	PR
C17			CR, PR	Yes	No	SD
C18			SD	Yes	-	SD
C19			PD	-	-	PD
C20			NE, No further evaluations			NE
C21	SD	Yes	CR, PR, SD, PD, NE, no more evaluation			SD
C22		No	CR, PR, SD	Yes	-	SD
C23			CR, PR, SD	No	-	NE
C24			PD	-	-	PD
C25			NE, No further evaluations			NE
C26	PD		-			PD
C27	NE	-	NE, No further evaluations			NE
C28		-	CR, PR, SD	Yes	-	SD
C29		-	CR, PR, SD	No	-	NE
C30		-	PD	-	-	PD

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

***If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR. If this response sequence occurs in the data set, 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]



Step 3: Unconfirmed Responses (for Interim Analysis Only)

For study where CR/PR confirmation is required, due to lack of sufficient follow-up time at interim analysis, both confirmed responders and unconfirmed responders will be reported. Subjects with any objective response (i.e., CR or PR) that is not confirmed as defined in Section 5.1.2 will be summarized based on below definitions.

Interim response of unconfirmed CR awaiting confirmatory scan:

A subject will have an interim response of unconfirmed CR awaiting confirmatory scan if and only if each of the following requirements is met: 1) the confirmed best overall response is not a confirmed CR and 2) the last evaluable tumor assessment prior to data cutoff (DCO) is a CR and 3) none of the following events are recorded (end of study date, death date, new anti-cancer therapy, end of radiographic follow up date, progression date).

Interim response of unconfirmed PR awaiting confirmatory scan:

A subject will have an interim response of unconfirmed PR awaiting confirmatory scan if and only if each of the following requirements is met: 1) the confirmed best overall response is not a confirmed CR and not a confirmed PR and 2) the last evaluable non-SD tumor assessment prior to data cutoff (DCO) is a PR and 3) none of the following events are recorded (end of study date, death date, new anti-cancer therapy, end of radiographic follow up date, progression date).

Interim response of unconfirmed response awaiting confirmatory scan:

A subject will have an interim unconfirmed response awaiting confirmatory scan if the subject has either an unconfirmed PR or an unconfirmed CR, awaiting a confirmatory scan.

Interim response of unconfirmed CR and not confirmed at next evaluable scan:

A subject will have an interim response of unconfirmed CR and not confirmed at next evaluable scan if and only if each of the following requirements is met: 1) the confirmed best overall response is not a confirmed CR and 2) any evaluable tumor assessment prior to data cutoff (DCO) is a CR and 3) either of the following occurs:

- **A CR is recorded at the last evaluable tumor assessment and any of the following events are recorded (end of study date, death date, new anti-cancer therapy, end of radiographic follow up date, progression date) or**
- **For any CR recorded prior to the last evaluable tumor assessment, the subsequent evaluable tumor assessment is never a CR.**

Interim response of unconfirmed PR and not confirmed at next evaluable scan:

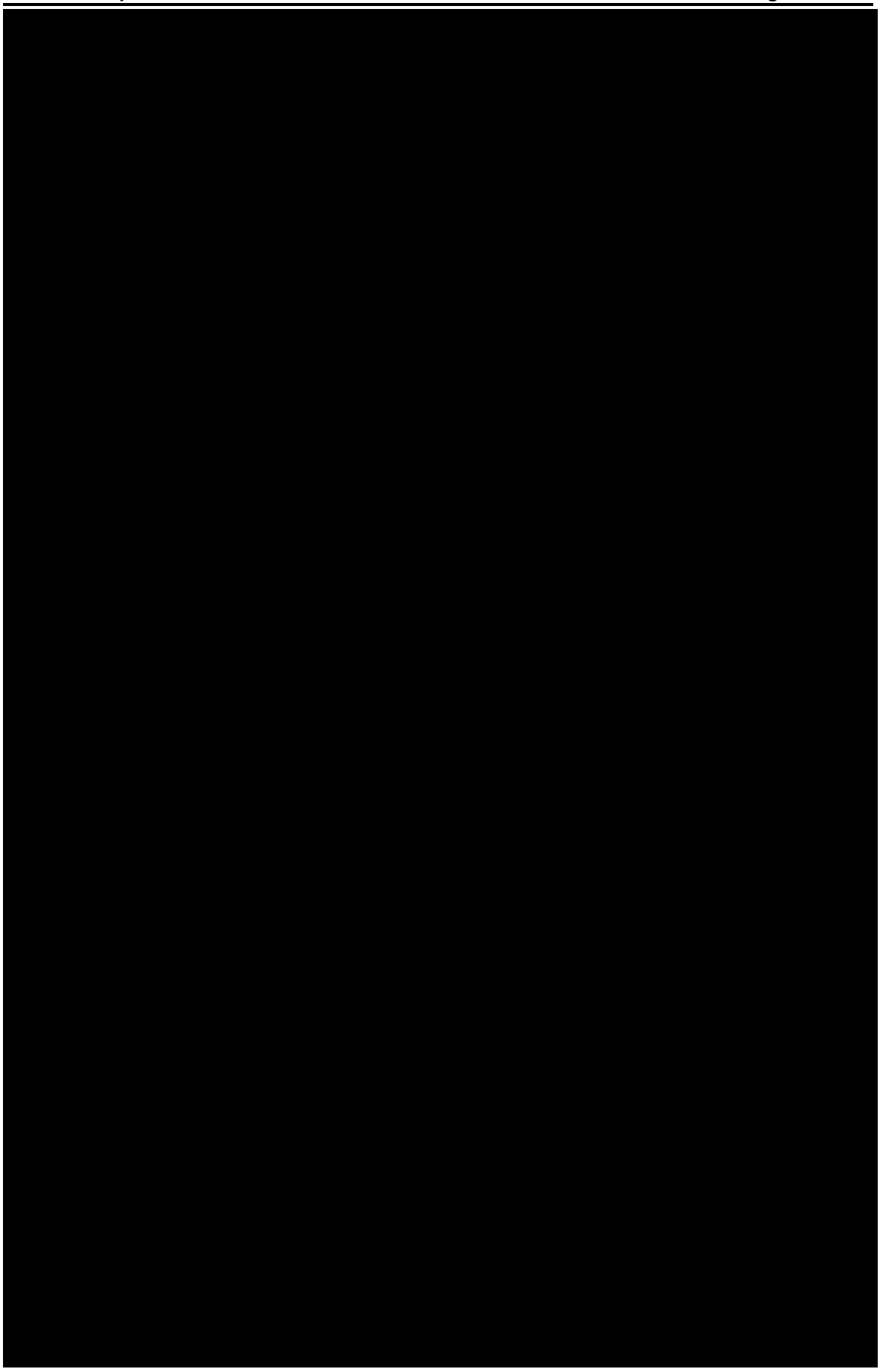
A subject will have an interim response of unconfirmed PR and not confirmed at next evaluable scan if and only if each of the following requirements is met: 1) the confirmed best overall response is not a confirmed CR and not a confirmed PR and 2) the subject does not have an interim response of unconfirmed CR and 3) any evaluable tumor assessment prior to data cutoff (DCO) is a PR and 4) either of the following occurs:

- **A PR is recorded at the last evaluable non-SD tumor assessment and any of the following events are recorded (end of study date, death date, new anti-cancer therapy, end of radiographic follow up date, progression date) or**
- **For any PR recorded prior to the last evaluable non-SD tumor assessment, the subsequent evaluable tumor assessment is never a PR or CR.**

Interim response of unconfirmed response and not confirmed at next scan:

A subject will have an interim unconfirmed response and not confirmed at next scan if the subject is classified as either unconfirmed PR or an unconfirmed CR, not confirmed at next scan.

[redacted]





[redacted]

Table 7. Radiographic Progression by RECIST 1.1 with PCWG3

RECIST1.1 Visit Response (soft tissue/visceral)[a]	Bone Progression Status	Bone Lesion (Present/Absent)	Radiographic Response by RECIST 1.1 with PCWG3 Modification
PD	Any	Any	PD
Any[d]	PDc	Any	PD[b]
Any except PD	PDu	Any	Unconfirmed 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 TL and NTLs at all visits), 'Undefined' in the 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 lesions 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 D. Modified Toxicity Probability Interval Design (mTPI-2)

For Part 2 (AMG 160 Combination with Pembrolizumab), trial monitoring rules are based on a modified toxicity probability interval design (mTPI-2). Prespecified monitoring rules are based on an extension of mTPI up-and-down design, mTPI-2, to determine the MTD with target DLT rate of 35 %. The mTPI-2 models the probability of toxicity for each dose level using a Bayesian model where each dose level has the same prior on the probability of toxicity, a Beta (1,1). The safety will be assessed based on mTPI-2 Dose Decision Outcomes with a 35% Target DLT Rate. When subjects are treated at the current dose level, the posterior probability of toxicity is updated using the observed data from this level. Dose level decisions are made based on this posterior probability of toxicity, using 3 toxicity probability intervals (TPI).

- Under-dosing TPI: DLT rate from 0 to $< 30\%$
- Target TPI: DLT rate from 30% to 40%
- Over-dosing: DLT rate $> 40\%$

For the current dose level and after adjusting for the width of the under-dosing TPI, if the DLT rate is most likely in the under-dosing TPI then the recommendation is to dose escalate. If the DLT rate is most likely in the target TPI then the recommendation is to stay at the current level. If the DLT rate is most likely in the over-dosing TPI then the recommendation is to de-escalate. If DLTs are observed, the maximum tolerated dose (MTD) is the dose level with a DLT toxicity rate closest to 35%.

All subjects who are enrolled and receive at least 1 dose of AMG 160 in combination with Pembrolizumab will be included in the analysis, unless otherwise specified. A formal interim analysis of available safety and efficacy data will occur when all remaining dose-escalation subjects have had the opportunity to complete 28 days on study. This interim analysis will estimate the MTD1 and MTD2 associated with the AMG 160 first step and target doses, support the determination of the RP2D, and support the evaluation of benefit/risk profile of AMG 160 plus Pembrolizumab.

Appendix E. Additional Definition

Information described below will be reported from eCRF.

Partial Response (PR)

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)

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)

At least a 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)

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

Non-CR/Non-PD

Persistence of one or more non-target lesion (s) and/or maintenance of tumor marker level above the normal limits.

Measurable baseline disease

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 scan or MRI. To be measurable a lymph node must be $\geq$15mm in short axis when assessed by CT scan or 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.”

Appendix F. Censoring Rules

Censoring rules for 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	Date of the first dose of investigational product (AMG 160 or Pembrolizumab)	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
Death or PD immediately after more than one consecutively missed tumor assessment**	Date of last evaluable radiographic tumor assessment prior to the missing assessments*	Censored

DCO: data cutoff; EOS: end of study; PD: progressive disease

* This supersedes the previous rules that result in Event at date of PD or death

**Implementation details: censoring with death or PD immediately after more than one consecutively missed tumor assessment

Scenarios of PD or Death	Censoring Rule	X Days in Censoring Rule
< Week 32	If PD or death is X days after the last scan, censor at the last scan	119
>= Week 32 but < Week 44		147

>= Week 44		175

Note: Study weeks of EOIP, SFU, LTFU can be converted using visit dates. **Bone scan progression is expected to be confirmed per protocol.**

Censoring rules for TTP (radiographic)

Situation up to DCO/EOS	**Date of Event or Censoring**	**Outcome**
No evaluable post-baseline or on-study disease assessment	Date of the first dose of investigational product (AMG 160 or Pembrolizumab)	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
PD immediately after more than one consecutively missed tumor assessment**	Date of last evaluable radiographic tumor assessment prior to the missing assessments*	Censored

DCO: data cutoff; EOS: end of study; PD: progressive disease

* This supersedes the previous rules that result in Event at date of PD

**Implementation details: censoring with PD immediately after more than one consecutively missed tumor assessment

Scenarios of PD or Death	Censoring Rule	X Days in Censoring Rule
< Week 32	If PD or death is X days after the last scan, censor at the last scan	119
>= Week 32 but < Week 44		147
>= Week 44		175

Note: Study weeks of EOIP, SFU, LTFU can be converted using visit dates. **Bone scan progression is expected to be confirmed per protocol.**

Censoring rules for DOR per RECIST 1.1:

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	Date of the first dose of investigational product (AMG 160 or Pembrolizumab)	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 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
Death or PD immediately after more than one consecutively missed tumor assessment**	Date of last evaluable tumor assessment by CT/MRI prior to the missing assessments*	Censored

DCO: data cutoff; EOS: end of study; PD: progressive disease

* This supersedes the previous rules that result in Event at date of PD or death

**Implementation details: censoring with death or PD immediately after more than one consecutively missed tumor assessment

Scenarios of PD or Death	Censoring Rule	X Days in Censoring Rule
< Week 32	If PD or death is X days after the last scan, censor at the last scan	119
>= Week 32 but < Week 44		147
>= Week 44		175

Note: Study weeks of EOIP, SFU, LTFU can be converted using visit dates. Bone scan progression is expected to be confirmed per protocol.

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); or, No evaluable baseline PSA assessment;	Date of the first dose of investigational product (AMG 160 or Pembrolizumab)	Censored
PSA progression	Date of PSA progression	Event
Death	Date of death	Event
All other scenarios	Date of last PSA assessment	Censored

DCO: data cutoff; EOS: end of study; PSA: prostate-specific antigen

Censoring rules for PSA DOR

Situation up to DCO/EOS	**Date of Event or Censoring**	**Outcome**
PSA progression after PSA response	Date of PSA progression	Event
Death after PSA response	Date of death	Event
All other scenarios	Date of last PSA assessment	Censored

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 160 or Pembrolizumab)	Censored

PSA progression	Date of PSA progression	Event
Completed study without PSA progression; or, on study without PSA Progression; or, Death; All other scenarios	Date of last PSA assessment	Censored

DCO: data cutoff; EOS: end of study; PSA: prostate-specific antigen